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SYNTHESIS AND STUDY THE PHARMACOLOGICAL ACTIVITY OF DERIVATIVES OF 5-DIMETHYLAMINOPYRANO[3,2-c]QUINOLIN-2-ONES

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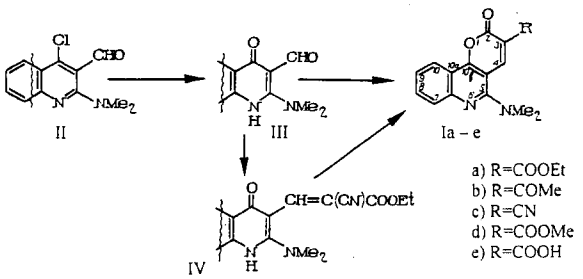
A simple method of synthesizing derivatives of 5-dimethylaminopyrano[3,2-c]quinolin-2-ones is proposed which involves obtaining 4-chloro- or 4-oxo-3-formylquinolines using compounds having an active methylene group. The pharmacological activity of the synthesized compounds is studied.

We showed previously [1] that intramolecular cyclization of α-cyano-β-(2-dimethylamino-4-chloroquinolin-3-yl)acrylonitrile in acetic acid smoothly leads to 2H-3-cyano-5-dimethylaminopyrano[3,2-c]quinolin-2-one (Ic). Bearing in mind that among the derivatives of this tricyclic system we discovered compounds having a pharmacological (in particular psychotropic) activity [2, 3], in the present work we studied the possibility of obtaining pyrano[3,2-c]quinolines (Ia – e) with various substituents in position 3 of the pyran ring. We also studied the pharmacological activity of these substances and of some intermediates in their synthesis for their psychotropic effect. Previously, compounds belonging to this heterocyclic system were synthesized by reacting 3-carbonyl- or 3-dialkylaminomethyl-4-quinolines with active methylene derivatives [4 – 7]. In particular, the condensation of 3-formyl-4-hydroxyquinolin-2-one with compounds having an active CH_2 group yielded derivatives of pyrano[3,2-c]quinoline having an oxo group in position 2 of the quinoline ring [5], while information is not available on synthesis of similar tricycles having a substituted amino group in position 2 (except for our paper [1] mentioned above). Since we recently developed an accessible method for synthesizing 4-chloro-3-formyl-2-dimethylaminoquinoline (II) [1], we selected it as the basic startting material for the present work. By treating the chloro derivative II with a concentrated NaOH solution, we synthesized the corresponding 4-oxo derivative (III). Condensation of the aldehyde III with compounds having an active methylene unit such as the ethyl ester of malonic acid or acetoacetic ester in benzene and in the presence of piperidine acetate leads in one step to the corresponding pyrano[3,2-c]quinolines Ia, b. Under somewhat different conditions, in the reaction of compound III with the ethyl ester of cyanoacetic acid in alcohol and in the presence of potassium carbonate, it is possible to isolate the intermediate (IV), which by cyclization in acetic acid is transformed into the 3-cyano derivative Ic which we described earlier in [1].



The compounds Ia, d were also obtained when boiling II with 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) in a medium of the appropriate alcohol and in the presence of catalytic amounts of triethylamine. The reaction proceeds via the stage of formation of the methylene derivative of (V), which can be isolated in high yield when aldehyde II reacts with Meldrum's acid in chloroform at 20°C.

It is interesting to note that the formation of Id is also observed when the dinitrile (VI) reacts with Meldrum's acid in methanol. In this case, too, the key intermediate is apparently the methylene derivative of V that forms from VI by displacement of the dicyanomethylene fragment by the Meldrum's acid residue. We described similar reactions in detail earlier in [1]. However, in an attempt to obtain Id by reacting quinoline III with Meldrum's acid in the same cases, only the methylene

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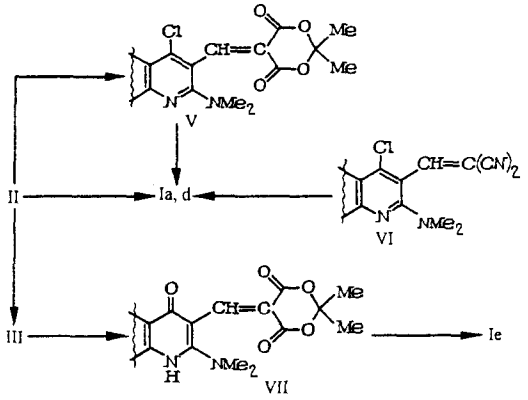
derivative of 4-oxoquinoline (VII) is isolated from the reaction mixture. Its further boiling leads to acid Ie, whereas the formation of Id is not observed at all in the reaction mixture (thin-layer chromatography). The acid Ie can also be obtained by briefly heating VII at 200 – 210°C.



The structure of the obtained compounds was confirmed by the results of IR and PMR spectroscopy. The IR spectra of Ia – e have absorption bands at 1750 – 1700 cm^{-1}, typical of the stretching vibrations of the C=O groups in esters or δ-lactones. A comparison of quinolinones and pyrano[3,2-c]quinolinones with the same type of substitution (e.g., IV and Ic, see *Experimental Part*) shows that the formation of the pyran ring is accompanied by a number of changes in the ^1H and ^{13}C NMR spectra, namely, significant chemical shifts of the signals from the methine proton in IV (δ = 8.53 ppm) and 4-H in Ic (δ = 8.97 ppm), and also of the signals from the carbon atom of the carbonyl group in IV (δ = 176.5 ppm) and C (10c) (δ = 160.4 ppm) in Ic.

CHEMICAL EXPERIMENTAL PART

The PMR spectra were obtained on a Varian XL-200 instrument, internal standard TMS, and the IR spectra were obtained on a Perkin – Elmer-599 spectrophotometer (USA) in the form of vaseline oil mulls. The mass spectra were obtained on a Varian-MAT-112 spectrometer with direct injection of the sample into the ion source (the energy of the ionizing electrons was 70 eV). The course of the reaction and the purity of the products were monitored by thin-layer chromatography on Silufol UV-254 plates in the systems $CHCl_3$, benzene – acetone, 9 : 1. The compounds are characterized in Table 1. The elemental analysis results correspond to the calculated values.

TABLE 1. Physicochemical Properties of Synthesized Compounds

Compound	Yield, %	M. p., °C*	Empirical formula	IR spectrum, ν_{max}, cm^{-1}
Ia	75	138 – 140	$C_{17}H_{16}N_2O_4$	1780, 1700(C=O)
Ib	60	121 – 122	$C_{16}H_{14}N_2O_3$	1750(C=O)
Id	64	168 – 170	$C_{16}H_{14}N_2O_4$	1760(C=O)
Ie	55	194 – 196	$C_{15}H_{12}N_2O_4$	1760(C=O)
III	51	242 – 244	$C_{12}H_{12}N_2O_2$	1670(C=O)
IV	74	214 – 216	$C_{17}H_{17}N_3O_3$	2200(C≡N), 1700(C=O)
V	61	174 – 175	$C_{18}H_{17}N_2ClO_4$	1730(C=O)
VII	75	202 – 205	$C_{18}H_{18}N_2O_5$	1710, 1670(C=O)

* Compounds Id, III, V, and VII were recrystallized from methanol, Ia and Ib – from alcohol, Ie from a mixture of methanol and DMFA, 8 : 2, IV from a mixture of water and alcohol, 1 : 1.

2-Dimethylamino-3-formyl-1,4-dihydroquinolin-4-one (III). We boiled a mixture of 0.23 g (1 mmole) of compound II, 10 ml of alcohol, and 10 ml of 25% NaOH for 1 h, cooled the reaction mixture to 0°C, added 10 ml of water and 5 ml of AcOH to a pH of 6.5 – 7. We filtered off the formed precipitate, washed it with water, and dried it. M^+ 216. ^1H NMR spectrum (δ, ppm, DMSO-d_6): 3.07 (s, NMe_2), 7.06 – 7.96 (m, 5, 6, 7, 8-H_4), 9.92 (s, CHO), 10.47 (s, H_1).

3-Ethoxycarbonyl-5-dimethylaminopyrano[3,2-c]quinolin-2-one (Ia). *Method A.* We boiled a mixture of 0.22 g (1 mmole) of III, 0.16 g (1 mmole) of the diethyl ester of malonic acid, 15 ml of benzene, 0.5 ml of AcOH and 0.1 ml of piperidine with removal of the azeotrope over the course of 1 h. We cooled the reaction mixture, distilled off the solvent under vacuum, chromatographed the residue in a column with silica gel, and eluted with $CHCl_3$. M^+ 312. ^1H NMR spectrum (δ, ppm, DMSO-d_6): 1.31 and 4.30 (t, q, $COOCH_2CH_2$), 3.12 (s, NMe_2), 7.42 – 8.07 (m, 7, 8, 9, 10-H_4), 8.70 (s, 4-H). ^{13}C NMR spectrum (δ, ppm, DMSO-d_6): 42.2 (s, NMe_2), 103.2 (4a-C), 114.3 (10a-C), 115.1 (3-C), 122.3 – 133.4 (7 – 10-C_4), 146.5 (4-C), 148.5 (6a-C), 155.6 (5-C), 158.1 (2-C), 160.5 (10b-C), 164.0 (COOH). *Method B.* To one gram (2.77 mmole) of V, we added 10 ml of abs. alcohol, a catalytic amount of triethylamine, and boiled the mixture for 1 h, cooled it, and filtered off the precipitate. We obtained 0.5 g (58%) of compound Ia, identical in its IR spectrum to the substance obtained by method A. PMR spectrum (δ ppm, DMSO-d_6): 2.61 (s, $COCH_3$), 3.14 (s, NMe_2), 7.40 – 8.06 (m, 7, 8, 9, 10-H_4), 8.62 (s, 4-H).

Ethyl ester of α-cyano-β-(2-dimethylamino-4-oxo-1,4-dihydroquinolin-3-yl)acrylic acid (IV). To a solution of 2.16 g (10 mmole) of quinoline III in 60 ml of abs. alcohol, we added 1.35 g (12 mmole) of the ethyl ester of cyanoacetic acid and 2 g of calcined potassium carbonate. We boiled the reaction mixture for 1 h, cooled it to 20°C, filtered it to remove inorganic impurities, evaporated the filtrate under vacuum, and recrystallized the precipitate from 50% alcohol. M^+ 311. PMR spectrum (δ, ppm, DMSO-d_6): 3.13 (s, NMe_2), 1.33 (t, $COOCH_2CH_3$), 4.30 (q, $COOCH_2CH_3$), 8.53 (s, CH–C(CN)COOEt), 11.0 (br. s, 1-H), 7.33 – 8.04 (m, 5, 6, 7, 8-H_4). ^{13}C NMR spectrum (δ, ppm, DMSO-d_6): 41.6 (s, NMe_2), 52.4 ($COOCH_2CH_3$),[2] 90.9 (2-C), 100.2 (3-C), 116.8 (CN), 120.1 – 132.2 (5 – 8-C_4), 123.1 (4a-C), 141.0 (8a-C), 158.6 (2-C), 165.5 (COOEt), 176.5 (4-C).

3-Cyano-5-dimethylaminopyrano[3,2-c]quinolin-2-one (Ic). We held a solution of 0.31 g (1 mmole) of IV in 5 ml of AcOH

[2] One of the signals of the substituent falls within the DMSO-d_6 signal at 39.6 ppm.

at 20°C for 1 h, added 10 ml of water, extracted the reaction mixture with $CHCl_3$ (2 × 10 ml), washed the organic layer with water, dried it over $CaCl_2$, evaporated the solvent under vacuum, and obtained 0.14 g (54%) of compound Ic, m. p. 210 – 213°C ([1], m. p. 212 – 213°C).

2-Dimethylamino-3-[(2,2-dimethyl-4,6-dioxo-1,3-dioxacyclohexane-5-ylidene)methyl]-4-chloroquinoline (V). To 1.2 g (5 mmole) of II in 20 ml of $CHCl_2$, we added 0.847 g (5.5 mmole) of Meldrum's acid and a catalytic amount of triethylamine. We mixed the reactants at 20°C for 2.5 h, distilled off the solvent under vacuum, chromatographed the residue in a column with silica gel, eluted with $CHCl_3$, and isolated 1.1 g (61%) of compound V. M^+ 360.

3-Methoxycarbonyl-5-dimethylaminopyrano[3,2-c]-quinolin-2-one (Id). *Method A.* To 0.56 g (2 mmole) of the nitrile of α-cyano-β-(2-dimethyl-amino-4-chloroquinoline-3-yl)acrylic acid (VI) in 20 ml of methanol, we added 0.36 g (2.5 mmole) of Meldrum's acid and a catalytic amount of triethylamine. We boiled the reaction mixture for 4 h, cooled it to room temperature, distilled off the solvent under vacuum, recrystallized the residue from methanol, and obtained 0.37 g (62%) of Id. M^+ 298. PMR spectrum (δ, ppm, DMSO-d_6): 3.11 (s, NMe_2), 3.85 (s, $COOCH_3$), 7.42 – 8.08 (m, 7, 8, 9, 10-H_4), 8.69 (s, 4-H). *Method B.* We obtained compound Id from V and methanol similarly to the synthesis of Ia by method B with a yield of 64%.

2,2-Dimethyl-5-[ylidenemethyl(2′-dimethylamino-4′-oxo-1′,4′-dihydroquinolin-3′-yl)]-1,3-dioxane-4,6-dione (VII). We boiled a mixture of 2.16 g (10 mmole) of quinoline III, 30 ml of methanol), 80 ml of $CHCl_3$, 1.44 g (10 mmole) of Meldrum's acid, and a catalytic amount of triethylamine for 1 h, evaporated the reaction mixture under vacuum, triturated the residue with 15 ml of cold methanol, filtered off the formed precipitate, washed it with cold methanol, and obtained 2.60 g of VII (75%). M^+ 342. PMR spectrum (δ, ppm, DMSO-d_6): 1.73 (s, Me_2), 3.06 (s, NMe_2), 7.29 – 7.99 (m, 7, 8, 9, 10-H_4), 8.41 (s, methine proton), 10.7 (br. s, 1-H). ^{13}C NMR spectrum (δ, ppm, DMSO-d_6): 26.9 (Me), 42.0 (s, NMe_2), 102.6 (5-C), 102.9 (2-C), 103.5 (3′-C), 118.1 – 138.2 (5′ – 8′-C), 122.3 (5′a-C), 138.2 (8′a-C), 150.1 (2-C), 158.5 (2′-C), 160.06, 164.1 (6-C, 4-C), 176.0 (4′-C).

5-Dimethylamino-2-oxopyrano[3,2-c]-3-quinoline carboxylic acid (Ie). *Method A.* We boiled a mixture of 0.32 g (1 mmole) of VII, 16 ml of $CHCl_3$, 6 ml of methanol, and a catalytic amount of triethylamine for 0.5 h, cooled it, evaporated the solvent under vacuum, dissolved the residue in a mixture of $CHCl_3$ – MeOH, 8 : 2, and chromatographed it in a column with silica gel. eluent $CHCl_3$ – MeOH, 8 : 2. M^+ 284. PMR spectrum (δ, ppm, DMSO-d_6): 3.12 (s, NMe_2), 7.46 – 8.15 (m, 7, 8, 9, 10-H_4), 8.69 (s, 4-H). *Method B.* We heated 1 g (3 mmole) of VII at 200 – 210°C for 1 – 2 min. We removed the flask with the reaction mixture from the bath, cooled it in air to room temperature. We dissolved the melt in 10 ml of $CHCl_3$ and chromatographed it as in A. We obtained 0.55 g (66%) of compound Ie.

PHARMACOLOGICAL EXPERIMENTAL PART

We studied the activity of the compounds Ib – d, IV, and VII in Porsolt's emotional-stressor behavior test and a number of neurochemical tests: from the response to reserpine, 5-hydroxytryptophan, levodopa, and tremorine. Moreover, we studied the antihypoxic properties of the compounds and their acute toxicity, and also the anticonvulsive activity of the carboxy derivatives.

The experiments were run with mice of both sexes with a mass of 18 – 20 g. The compounds being studied were administered 60 min before putting the animals into the water (the Porsolt test) or into a sealed chamber (antihypoxic effect), using maximum electrical shock (MES), or introducing only neurochemical analyzer: reserpine – 2.5 mg/kg intraperitoneally, tremorine – 20 mg/kg subcutaneously, levodopa – 200 mg/kg intraperitoneally, 5-hydroxytryptophan – 50 mg/kg intraperitoneally.

It was found (Table 2) that all the studied compounds have an activating effect, which can be judged by the reduction of the immobility of the animals in the behavior test, by the decrease in the reserpine effects, in particular, blepharoptosis, by

TABLE 2. Pharmacological Activity of Compounds Ib – d, IV, and VII

Compound	Internal dose, mg/kg	Number of rotations of water wheel per mouse after immersion in water during first 6 min	Blepharoptosis in scale units in 4 h after introducing reserpine, 2.5 mg/kg intraperiotoneally	Rectal temperature (°C) in 0.5 h after introducing levodopa 200 mg/kg intraperitoneally	Ratio of number of mice survived after MES to total number	Lifespan of one mouse in sealed chamber 8	LD_{50}, mg/kg
Distilled water	–	36 ± 4.1	3.6 *± 0.18	36.0 ± 0.35	1/10	38 ± 0.9	–
Ib	25	57 ± 2.3	1.8 ± 0.32*	37.6 ± 0.3	1/10	42 ± 1.2	> 750
Ic	25	50 ± 2.9	1.6 ± 0.36	37.6 ± 0.32	–	37 ± 0.8	> 750
Id	25	58 ± 2.5	2.3 ± 0.2*	37.7 ± 0.28	–	35 ± 1.4	> 750
IV	25	40 ± 3.6	3.4 ± 0.24	39.2 ± 0.24*	–	41 ± 0.9	> 750
	100	–	–	–	5/10	–	–
VII	25	37 ± 3.7	2.6 ± 0.24	39.1 ± 0.26*	–	36 ± 1.2	> 750

* Authentic at $p < 0.05$.

the increase in the hyperthermal effect of levodopa and the convulsive effect of 5-hydroxytryptophan. All these effects were noted when the compounds were administered in a dose of 25 mg/kg. At doses of 25 – 50 mg/kg, the compounds have a tendency to exhibit an antihypoxic effect (the increase in the lifespan in a sealed chamber under the influence of the studied compounds is not statistically authentic); at doses of 100 – 200 mg/kg, the compounds Id and IV exhibit an anticonvulsive effect.

Consequently, the derivatives of 5-dimethylamino[3,2-c]quinolin-2-ones Ib – d and also intermediates in their synthesis IV and VII exhibit a psychotropic property, which makes the further search for biologically active compounds in this series promising.

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