

Heterocyclic Ketones in the Pfitzinger Reaction

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Abstract—By the reaction of isatin with heterocyclic ketones (*N*-*tert*-butoxycarbonyl derivatives of pyrrolidin-3-one, piperidin-4-one, piperidin-3-one, 1,2,3,4-tetrahydroquinolin-4-one, 8-azabicyclo[3.2.1]octan-3-one, tetrahydropyran-4-one, tetrahydrobenzopyran-4-one) in the presence of KOH (the Pfitzinger reaction) were synthesized quinoline-4-carboxylic acids [4,3]fused with the respective heterocycles. These acids were involved in the reactions with diazomethane and amines at the carboxy group leading to methyl esters and amides, respectively. The esters obtained reacted with hydrazine hydrate affording the acid hydrazides, which entered in the condensation with benzaldehyde to form phenylhydrazones. The esters and amides containing *N*-*tert*-butoxycarbonyl fragment lost the *tert*-butoxycarbonyl group easily to form the secondary amines dihydrochlorides, the [4,3]fused quinoline-4-carboxylic acid derivatives.

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The Pfitzinger reaction consists in the interaction of isatin or its derivatives with α -hydrogen-containing ketones in strongly alkaline medium to form the corresponding cinchoninic acids [1, 2]. These compounds and their derivatives, apart from their research significance, are also of great practical interest, since among them drugs were found with a broad spectrum of biological activity [3–7]. In particular, it is established [4] that 2-(4-bromophenyl)quinoline-4-carboxylic acid is a selective inhibitor of the *C. albicans* prolyl tRNA synthetase, and 2-phenylquinolin-4-carboxamides may be used as analgesics, tranquilizers, antitumor and tuberculocidal drugs [6, 7].

Analysis of published data [8–19] shows that in the Pfitzinger reaction α -hydrogen ketones can be used with a variety of substituents, including carbocyclic derivatives: cyclohexanone [16–18], 1-indanone, and α -tetralone [17]. As a result of these reactions the 2-substituted, 2,3-disubstituted and [2,3]fused with carbocycles quinoline-4-carboxylic acids were obtained.

In this study, we first involved in the Pfitzinger reaction a number of heterocyclic compounds containing in the ring the $-\text{CH}_2-\text{CO}-$ fragment. For this purpose we used *N*-*tert*-butoxycarbonyl-substituted (Boc-substituted) pyrrolidin-3-one (**I**), piperidin-4-one (**II**), piperidin-3-one (**III**), 1,2,3,4-tetrahydroquinolin-4-one

(**IV**), and 8-azabicyclo[3.2.1]octan-3-one (**V**), as well as ketones with the oxygen-containing rings: tetrahydropyran-4-one (**VI**) and tetrahydrobenzopyran-4-one (**VII**). While selecting these heterocycles, we accounted for their biological significance as a pharmacophore fragments contributing to the structure of many pharmaceuticals [20, 21].

We found that the Pfitzinger reaction proceeds smoothly at boiling ketones **I–VII** taken in a small excess (5–10%) with isatin in the presence of a tenfold excess of KOH in a dioxane–water 1:1 mixture for 10–12 h. However, the composition of the formed reaction products significantly depended on the structure of the parent ketones. With compounds **II**, **IV–VII** individual heterocycles **VIII–XII** formed. Their composition and structure were confirmed by elemental analysis, GC–MS spectra (Table 1), IR and ^1H NMR spectra (Table 2) (Scheme 1).

Reaction of ketones **I** and **III** with isatin under the conditions of the Pfitzinger reaction led to a mixture (according to GC–MS and ^1H NMR spectra) of isomeric products **XIII–XVI**, due to the possibility of the condensation of intermediately formed isatinic acid potassium salt **A** at both α -methylene groups contiguous to the carbonyl carbon atom of these ketones (Scheme 2).

Table 1. Yields, melting points, data of elemental analysis and gas chromatography–mass spectrometry of compounds **VIII–XXXVIII**

Comp. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %			Mass spectrum, m/z		Calculated M
			C	H	N		C	H	N	$M + 1$	$M - 101 + 1$	
VIII	86	178–179	65.58	5.93	8.47	$C_{18}H_{20}N_2O_4$	65.82	6.10	8.54	329	228	328
IX	45	201–202	68.23	4.75	6.18	$C_{13}H_{11}NO_3$	68.12	4.80	6.11	230		229
X	78	230–232	70.04	5.59	7.38	$C_{22}H_{20}N_2O_4$	70.21	5.32	7.45	377	276	376
XI	27	252–254	73.42	4.06	4.96	$C_{17}H_{11}NO_3$	73.65	3.97	5.05	278		277
XII	82	161–162	67.73	6.34	7.85	$C_{20}H_{22}N_2O_4$	67.80	6.21	7.91	355	254	354
XIII+XI	54	170–176	65.12	5.87	8.96	$C_{17}H_{18}N_2O_4$	64.97	5.73	8.92	315	214	314
V	55	148–154	65.68	5.94	8.62	$C_{18}H_{20}N_2O_4$	65.85	6.10	8.54	329	228	328
XV+XVI	86	61–62	66.52	6.31	8.06	$C_{19}H_{22}N_2O_4$	66.67	6.43	8.19	343	242	342
XVII	83	oil	69.28	5.17	5.83	$C_{14}H_{13}NO_3$	69.14	5.35	5.76	244		243
XVIII	85	92–93	70.61	5.46	7.03	$C_{23}H_{22}N_2O_4$	70.77	5.64	7.18	391	290	390
XIX	81	54–55	74.28	4.39	4.67	$C_{18}H_{13}NO_3$	74.23	4.47	4.81	292		291
XX	78	65–66	68.24	6.41	7.69	$C_{21}H_{24}N_2O_4$	68.48	6.52	7.61	369	268	368
XXI	56	161–162	65.86	6.34	12.93	$C_{18}H_{21}N_3O_3$	66.06	6.42	2.84	328	227	327
XXII	48	136–138	68.41	5.18	12.17	$C_{13}H_{12}N_2O_2$	68.42	5.26	12.28	229		228
XXIII	60	156–157	68.09	6.43	11.85	$C_{20}H_{23}N_3O_3$	67.99	6.52	11.90	354	253	353
XXIV	78	136–137	64.52	6.78	11.26	$C_{20}H_{25}N_3O_4$	64.69	6.74	11.32	372	271	371
XXV	64	96–97	66.36	5.96	10.40	$C_{15}H_{16}N_2O_3$	66.18	5.88	10.29	273		272
XXVI	62	112–113	66.38	6.67	10.73	$C_{22}H_{27}N_3O_4$	66.50	6.80	10.58	398	297	397
XXVII	98	181–182	63.17	6.52	16.28	$C_{18}H_{22}N_4O_3$	63.16	6.43	16.37	343	242	342
XXVIII	96	148–149	64.32	5.21	17.43	$C_{13}H_{13}N_3O_2$	64.20	5.35	17.28	244		243
XXIX	98	155–156	65.14	6.39	15.08	$C_{20}H_{24}N_4O_3$	65.22	6.52	15.22	369	268	368
XXX	80	198–200	69.63	5.93	13.26	$C_{25}H_{26}N_4O_3$	69.77	6.05	13.02	431	330	430
XXXI	81	158–160	72.37	5.24	12.61	$C_{20}H_{17}N_3O_2$	72.51	5.14	12.69	332		331
XXXII	86	181–182	70.83	6.02	12.13	$C_{27}H_{28}N_4O_3$	71.05	6.14	12.28	457	356	456
XXXIII	99	223–225	53.62	4.85	8.73	$C_{14}H_{14}N_2O_2 \cdot 2 HCl$	53.33	5.08	8.89	243		242
XXXIV	96	287–289	59.38	4.26	7.61	$C_{18}H_{14}N_2O_2 \cdot 2 HCl$	59.50	4.41	7.71	291		290
XXXV	98	273–275	56.17	5.34	8.26	$C_{16}H_{16}N_2O_2 \cdot 2 HCl$	56.30	5.28	8.21	269		268
XXXVI	98	293–295	51.87	5.08	14.11	$C_{13}H_{13}N_3O \cdot 2 HCl$	52.00	5.00	14.00	228		227
XXXVII	99	301–304	55.43	5.16	12.74	$C_{15}H_{15}N_3O \cdot 2 HCl$	55.21	5.21	12.88	254		253
XXXVIII												

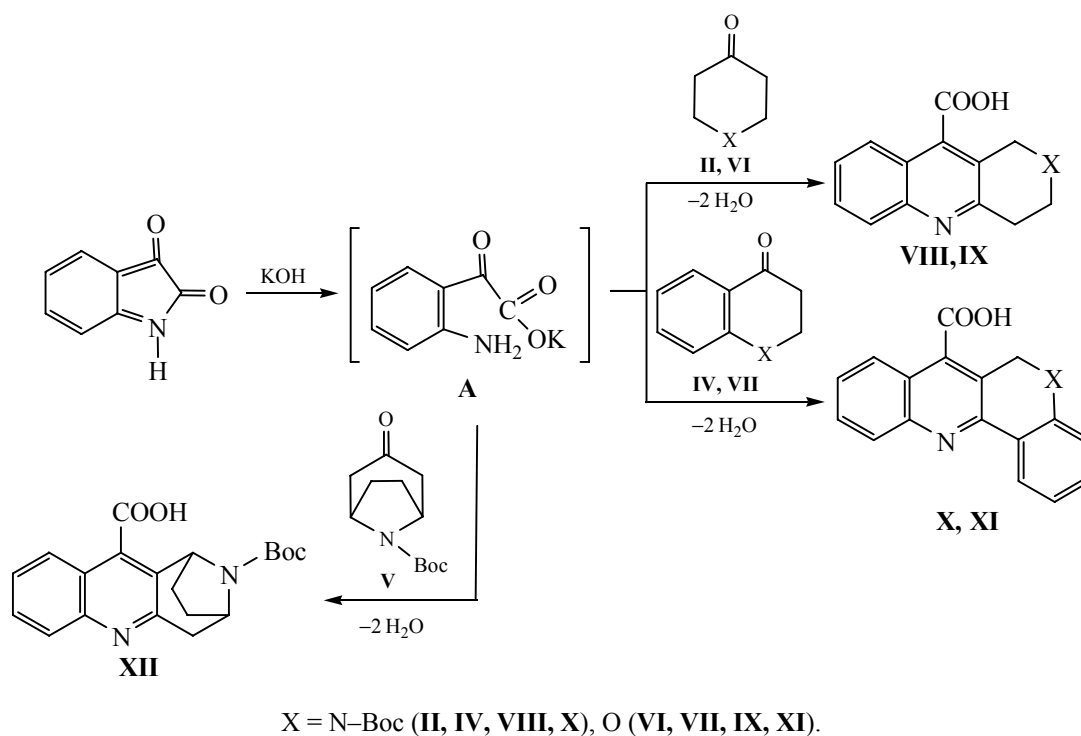
Table 2. Spectral data of compounds **VIII–XXXVIII**

Comp. no.	IR spectrum, ν , cm^{-1}	1H NMR spectrum, δ , ppm
VIII	1681, 1704 (C=O), 2948 (OH)	1.40 s (9H, 3 CH ₃), 3.12 d (2H, CH ₂), 3.74 d (2H, NCH ₂), 4.76 s (2H, NCH ₂), 7.65 t (1H, H ⁶ quinoline), 7.75 t (1H, H ⁷), 7.86 d (1H, H ⁵), 7.97 d (1H, H ⁸), 13.95 br.s (1H, COOH)
IX	1708 (C=O), 2936 (OH)	3.15 d (2H, CH ₂), 4.09 d (2H, OCH ₂), 4.90 s (2H, OCH ₂), 7.59 t (1H, H ⁶ quinoline), 7.74 t (1H, H ⁷), 7.91 d (1H, H ⁵), 7.96 d (1H, H ⁸), 13.92 br.s (1H, COOH)
X	1682, 1702 (C=O), 2945 (OH)	1.41 s (9H, 3 CH ₃), 4.72 s (2H, NCH ₂), 7.02–7.21 m (4H, C ₆ H ₄), 7.64 t (1H, H ⁶ quinoline), 7.78 t (1H, H ⁷), 7.88 d (1H, H ⁵), 7.97 d (1H, H ⁸), 13.92 br.s (1H, COOH)
XII	1700 (C=O), 2938 (OH)	4.92 s (2H, OCH ₂), 7.04–7.23 m (4H, C ₆ H ₄), 7.61 t (1H, H ⁶ quinoline), 7.75 t (1H, H ⁷), 7.91 d (1H, H ⁵), 7.98 d (1H, H ⁸), 13.92 br.s (1H, COOH)
XII	1685, 1705 (C=O), 2893 (OH)	1.38 s (9H, 3 CH ₃), 1.46–1.85 m (4H, 2 CH ₂), 3.06 d (2H, CH ₂), 4.53 m (1H, H), 4.83 s (1H, CH), 7.66 t (1H, H ⁶ quinoline), 7.75 t (1H, H ⁷), 7.85 d (1H, H ⁵), 7.98 d (1H, H ⁸), 14.03 br.s (1H, COOH)

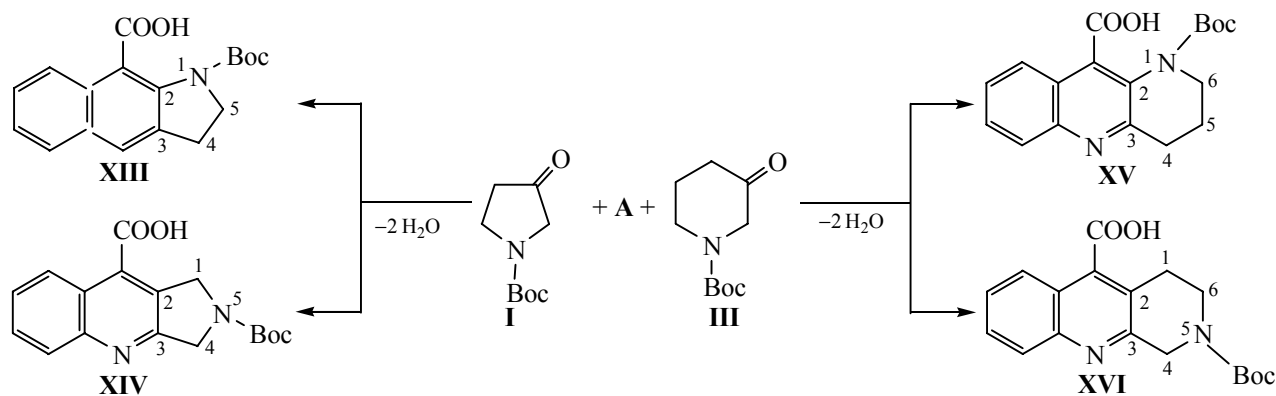
Table 2. (Contd.)

Comp. no.	IR spectrum, ν , cm^{-1}	^1H NMR spectrum, δ , ppm
XIII+XI	1684, 1702, 1707 (C=O),	1.39–1.43 d (9H, 3 CH ₃), 3.31 d (0.65 CH ₂), 3.75–4.58 m (2H, NCH ₂), 4.82 s (0.35 NCH ₂),
V	2924, 2954, 3002 (OH)	7.52–7.98 m (4H, quinoline), 13.87 br.s (1H, COOH)
	1682, 1700, 1708 (C=O),	1.40–1.45 d (9H, 3 CH ₃), 1.93 m (0.6 CH ₂), 2.92–3.05 m (2H, CH ₂), 3.52–3.68 m (2H, NCH ₂), 4.74 s (0.4 NCH ₂), 7.48–8.01 m (4H, quinoline), 13.95 br.s (1H, COOH)
XV+XVI	2932, 2968 (OH)	1.40 s (9H, 3 CH ₃), 3.11 d (2H, CH ₂), 3.74 d (2H, NCH ₂), 3.96 s (3H, OCH ₃), 4.78 s (2H, NCH ₂), 7.64 t (1H, H ⁶ quinoline), 7.75 t (1H, H ⁷), 7.87 d (1H, H ⁵), 7.98 d (1H, H ⁸)
XVII	1683, 1715 (C=O)	3.16 d (2H, CH ₂), 4.01 s (3H, OCH ₃), 4.12 d (2H, OCH ₂), 4.91 s (2H, OCH ₂), 7.48 t (1H, H ⁶ quinoline), 7.73 t (1H, H ⁷), 7.92 d (1H, H ⁵), 7.98 d (1H, H ⁸)
XVIII	1718 (C=O)	1.41 s (9H, 3 CH ₃), 3.95 s (3H, OCH ₃), 4.73 s (2H, NCH ₂), 7.01–7.20 m (4H, C ₆ H ₄), 7.63 t (1H, H ⁶ quinoline), 7.78 t (1H, H ⁷), 7.89 d (1H, H ⁵), 7.98 d (1H, H ⁸)
XIX	1685, 1716 (C=O)	4.02 s (3H, OCH ₃), 4.94 s (2H, OCH ₂), 7.03–7.24 m (4H, C ₆ H ₄), 7.61 t (1H, H ⁶ quinoline), 7.78 t (1H, H ⁷), 7.94 d (1H, H ⁵), 8.00 d (1H, H ⁸)
XX	1718 (C=O)	1.39 s (9H, 3 CH ₃), 1.44–1.86 m (4H, 2 CH ₂), 3.07 d (2H, CH ₂), 3.98 s (3H, OCH ₃), 4.73 s (3H, OCH ₃), 4.23 m (1H, CH), 4.84 s (1H, CH), 7.66 t (1H, H ⁶ quinoline), 7.74 t (1H, H ⁷), 7.84 d (1H, H ⁵), 7.98 d (1H, H ⁸)
XXI	1682, 1714 (C=O)	1.41 s (9H, 3 CH ₃), 3.12 d (2H, CH ₂), 3.75 d (2H, NCH ₂), 4.77 s (2H, NCH ₂), 7.63–7.98 m (4H, quinoline), 8.14 m (2H, CONH ₂)
XXII	1688, 1702, 1710 (C=O),	3.15 d (2H, CH ₂), 4.08 d (2H, OCH ₂), 4.90 s (2H, OCH ₂), 7.58–7.96 m (4H, quinoline), 8.16 m (2H, CONH ₂)
XXIII	3410–3428 (NH ₂)	1.38 s (9H, 3 CH ₃), 1.47–1.84 m (4H, 2 CH ₂), 3.07 d (2H, CH ₂), 4.24 m (1H, CH), 4.85 s (1H, CH), 7.64–7.98 m (4H, quinoline), 8.09 m (2H, CONH ₂)
	1700, 1714 (C=O),	1.40 s (9H, 3 CH ₃), 3.10 d (2H, CH ₂), 3.19 s (3H, NCH ₃), 3.65 s (3H, OCH ₃), 3.76 d (2H, NCH ₂), 4.78 s (2H, NCH ₂), 7.63–7.95 m (4H, quinoline)
XXIV	3412–3438 (NH ₂)	3.14 d (2H, CH ₂), 3.18 s (3H, NCH ₃), 3.71 s (3H, OCH ₃), 4.10 d (2H, OCH ₂), 4.92 s (2H, OCH ₂), 7.58–7.96 m (4H, quinoline)
	1685, 1698, 1712 (C=O),	1.39 s (9H, 3 CH ₃), 1.45–1.86 m (4H, 2 CH ₂), 3.05 d (2H, CH ₂), 3.20 s (3H, NCH ₃), 3.72 s (3H, OCH ₃), 4.22 m (1H, CH), 4.83 s (1H, CH), 7.68–8.01 m (4H, quinoline)
XXV	3410–3432 (NH ₂)	1.40 s (9H, 3 CH ₃), 3.10 d (2H, CH ₂), 3.70 d (2H, NCH ₂), 4.78 s (2H, NCH ₂), 5.72 s (2H, NH ₂), 7.68–8.03 m (4H, quinoline), 9.38 s (1H, NH)
XXVI	1682, 1702, 1715 (C=O)	3.17 d (2H, CH ₂), 4.09 d (2H, OCH ₂), 4.93 s (2H, OCH ₂), 5.81 s (2H, NH ₂), 7.61–8.04 m (4H, quinoline), 9.43 s (1H, NH)
XXVII	1703, 1715 (C=O)	1.39 s (9H, 3 CH ₃), 1.48–1.87 m (4H, 2 CH ₂), 3.08 d (2H, CH ₂), 4.25 m (1H, CH), 4.85 s (1H, CH), 5.64 s (2H, NH ₂), 7.68–8.02 m (4H, quinoline), 9.26 s (1H, NH)
XXVIII	1686, 1700, 1712 (C=O)	1.41 s (9H, 3 CH ₃), 3.11 d (2H, CH ₂), 3.73 d (2H, NCH ₂), 4.77 s (2H, NCH ₂), 7.12–7.33 m (5H, C ₆ H ₅), 7.66–7.98 m (4H, quinoline), 9.12 s (1H, =CH), 9.36 s (1H, NH)
XXIX	1684, 1698, 1705 (C=O),	3.15 d (2H, CH ₂), 4.08 d (2H, OCH ₂), 4.92 s (2H, OCH ₂), 7.14–7.36 m (5H, C ₆ H ₅), 7.61–7.98 m (4H, quinoline), 9.12 s (1H, =CH), 9.31 s (1H, NH)
XXX	3415–3486 (N–H)	1.38 s (9H, 3 CH ₃), 1.47–1.86 m (4H, 2 CH ₂), 3.05 d (2H, CH ₂), 4.24 m (1H, CH), 4.85 s (1H, CH), 7.10–7.28 m (5H, C ₆ H ₅), 7.64–8.02 m (4H, quinoline), 9.08 s (1H, =CH), 9.28 s (1H, NH)
	1701, 1712 (C=O),	3.18 d (2H, CH ₂), 3.91 m (2H, NCH ₂), 4.08 s (3H, OCH ₃), 4.97 d (2H, NCH ₂), 7.84–8.63 m (4H, quinoline), 12.08 br.s (2H, ⁺ NH ₂)
XXXI	3418–3508 (N–H)	4.10 s (3H, OCH ₃), 4.96 d (2H, NCH ₂), 7.24–7.36 m (4H, C ₆ H ₄), 7.86–8.63 m (4H, quinoline), 12.12 br.s (2H, ⁺ NH ₂)
	1682, 1704 (C=O),	1.52–1.98 m (4H, 2 CH ₂), 3.18 d (2H, CH ₂), 4.08 s (3H, OCH ₃), 4.86 m (1H, CH), 5.29 m (1H, CH), 7.84–8.53 m (4H, quinoline), 12.15 br.s (2H, ⁺ NH ₂)
XXXII	3420–3497 (N–H)	3.31 d (2H, CH ₂), 4.13 m (2H, NCH ₂), 5.03 m (2H, NCH ₂), 7.86–8.54 m (4H, quinoline), 8.44 m (2H, CONH ₂), 12.16 br.s (2H, ⁺ NH ₂)
	1628 (C=N), 1684, 1708 (C=O),	1.56–1.97 m (4H, 2 CH ₂), 3.20 d (2H, CH ₂), 4.91 m (1H, CH), 5.31 m (1H, CH), 7.83–8.56 m (4H, quinoline), 8.51 m (2H, CONH ₂), 12.11 br.s (2H, ⁺ NH ₂)
XXXIII	3436 (N–H)	
	1632 (C=N), 1702, 1714 (C=O),	
XXXIV	3442 (N–H)	
	1630 (C=N), 1682, 1705 (C=O),	
XXXV	3456 (N–H)	
	1720 (C=O), 3520–3640 (⁺ NH ₂)	
XXXVI		
	1722 (C=O), 3528–3654 (⁺ NH ₂)	
XXXVII		
	1720 (C=O), 3534–3684 (⁺ NH ₂)	
XXXVIII		
	1710 (C=O), 3248 (N–H),	
XXXIX	3564–3648 (⁺ NH ₂)	
	1712 (C=O), 3265 (N–H),	
XL	3568–3664 (⁺ NH ₂)	

Scheme 1.



Scheme 2.



Unfortunately, we were unable to separate individual compounds from the resulting mixtures of the products, as they have almost the same chromatographic mobility. Nevertheless, we identified the quantitative content of the isomers **XIII**, **XIV** and **XV**, **XVI**, respectively, on the basis of GC–MS and ^1H NMR spectra. The latter for the individual compounds **VIII**–**XII** are characterized by distinct multiplets that related uniquely to the corresponding protons of the structural fragments (Table 2). At the same time in the ^1H NMR spectra of the mixtures of compounds **XIII**,

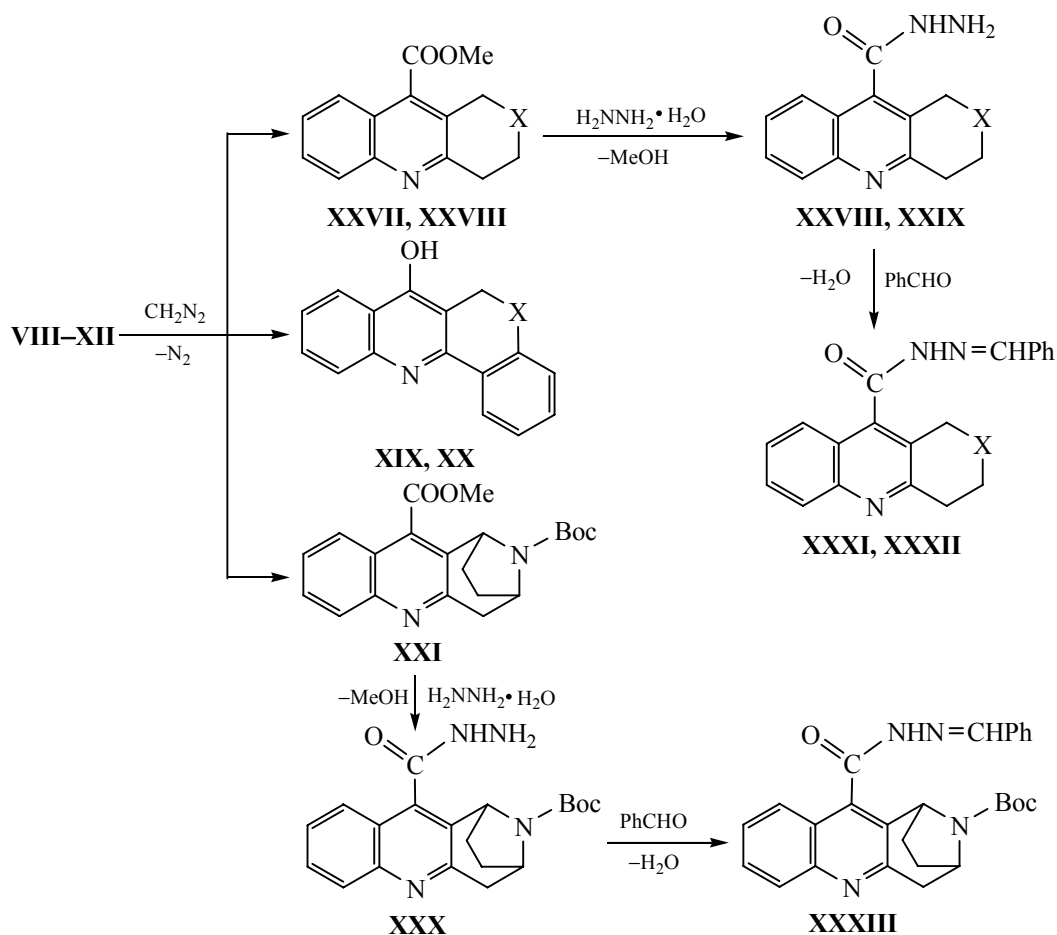
XIV and **XV**, **XVI** the signals of the quinoline skeleton are present as doubled signals, and in the resonance region of aliphatic protons there are signals related to both structures of the corresponding individual compounds **XIII**–**XVI**. In particular, the spectrum of a mixture of compounds **XIII** and **XIV** contains a doublet in the strong magnetic field at 3.31 ppm, which characterizes the β -protons (2H) in the $\text{CH}_2\text{CH}_2\text{N}$ fragment of compound **XIII** with relative integral intensity ~ 0.65 . This spectrum contains also a singlet in a weaker field at 4.82 ppm attributable

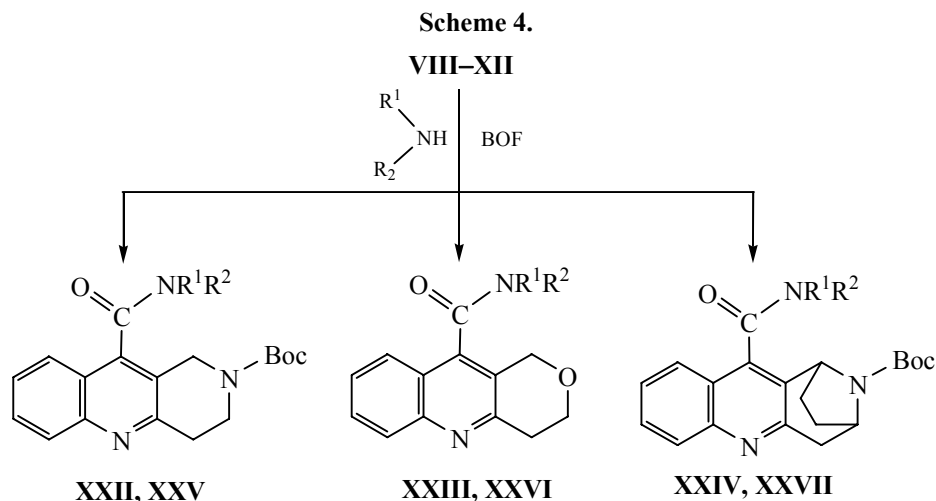
to the protons (2H) in the fragment of $\text{N}=\text{C}-\text{CH}_2-\text{N}$ of compound **XIV** with relative integral intensity ~ 0.35 . Consequently, the ratio of compounds **XIII**:**XIV** in the mixture is 65:35. This result was also confirmed by the GC-MS spectrum containing two peaks with the integral intensities reflecting the quantitative ratio of substances with similar molecular weight 32:18. A similar analysis of ^1H NMR spectrum (Table 2) of a mixture of compounds **XV** and **XVI** leads to the ratio of the isomers $\sim 3:2$. Thus, in the course of the Pfitzinger reaction the condensation of compounds **I** and **III** at the carbonyl group of the intermediate **A** proceeds predominantly with the participation of hydrogen atoms in the $\text{N}-\text{CH}_2-\text{C}=\text{O}$ fragment. This is probably due to the higher mobility of these hydrogen atoms because at the negative inductive effect of the nitrogen atom. A similar effect of oxygen was observed in the case of reaction of methyl aryloxymethylene ketones with isatin under the conditions of the Pfitzinger reaction [22]: 2-Methyl-3-aryloxyquinoline-4-carboxylic acids formed as a result

of condensation of aryloxymethylene group with the carbonyl group of the intermediate **A**.

Next, we studied some chemical transformations of the synthesized acids **VIII–XII** confirming their structures. In particular, by the reaction with diazomethane they were easily converted into the corresponding methyl esters **XXVII–XXI** (Scheme 3). The reaction of acid **VIII**, **IX**, and **XII** with amines (ammonia and *N*-methyl-*N*-methoxyamine) in the presence of a dehydrating reagent, benzotriazol-1-yloxy-tris(di-methylamino)phosphonium hexafluorophosphate (BOF), leads to the primary (**XXII–XXIV**) and tertiary (**XXV–XXVII**) amides respectively, possessing the scientific and practical interest (Scheme 4). The boiling of ethers **XVII**, **XVIII**, and **XXI** with hydrazine-hydrate in ethanol produces hydrazides **XXVIII–XXX**, which condense with benzaldehyde affording the corresponding phenylhydrazones **XXXI–XXXIII** (Scheme 3).

Scheme 3.





X = N-Boc (XVII, XIX, XXVIII, XXXI), O (XVIII, XX, XXIX, XXXII); $\text{R}^1 = \text{R}^2 = \text{H}$ (XXII–XXIV); $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{OMe}$ (XXV–XXVII).

Finally, at treating esters XVII, XIX, and XXI, and amides XXII and XXIV, containing the Boc group, with hydrogen chloride in anhydrous dioxane this group was removed to afford the secondary amine dihydrochlorides XXXIV–XXXVIII in almost quantitative yields (Scheme 5).

The composition and structure of compounds XVII–XXXVIII were confirmed by elemental analysis, GC–MS spectra (Table 1), IR and ^1H NMR spectra (Table 2).

It should be noted in conclusion that the compounds obtained containing functional groups can be used as reagents in combinatorial organic syntheses of new substances of the quinoline series with a view to their total screening for revealing biological activity.

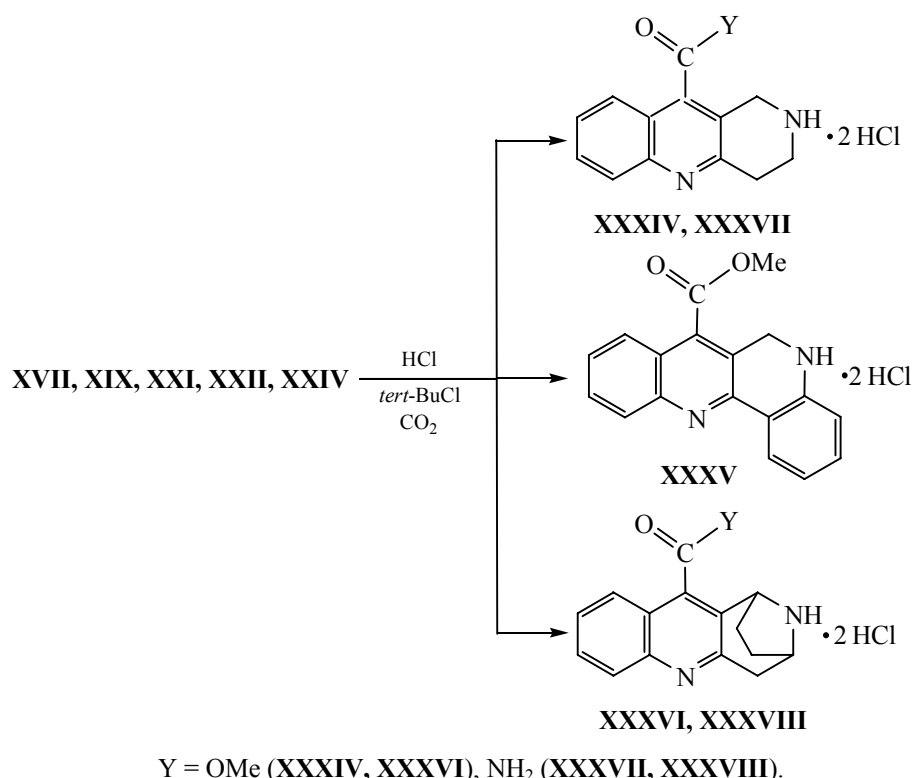
EXPERIMENTAL

IR spectra of the compounds were recorded on a Specord 75 IR spectrometer from the mulls in mineral oil. ^1H NMR spectra were recorded on a Varian Mercury Plus-400 spectrometer (400 MHz) from solutions in CDCl_3 (XVII–XXXIII) or in $\text{DMSO}-d_6$ (VIII–XVI, XXXIV–XXXVIII), internal reference HMDS. The GC–MS spectra were recorded on a Surveyor MSQ Thermo Finnigan (USA) instrument using chemical ionization at atmospheric pressure. Identity and purity of the compounds obtained was monitored by TLC on Silufol UV-254 plates, eluent hexane–ethyl acetate, 1:2, development under the UV light.

1-*tert*-Butoxycarbonylpiperidino[4,3-*c*]quinoline-4-carboxylic acid (VIII). A mixture of 1.47 g of isatin and 5.6 g of KOH in 20 ml of 50% aqueous dioxane was stirred for 20 min, then 2.40 g of *N-tert*-butoxycarbonylpiperidin-4-one (II) in 10 ml of the same solvent was added, and the reaction mixture was refluxed for 11 h. Then 60 ml of water was added, and aqueous solution was washed with 30 ml of benzene, 30 ml of diethyl ether, and acidified with concentrated hydrochloric acid (~ 7.4 ml) to pH 2–3. The precipitate formed was filtered off, washed with 40 ml of water, and dried to a constant weight. 2.82 g (86%) of compound VIII was obtained. By the same procedure were synthesized compounds IX, X, and XII.

1,2,3,4-Tetrahydrobenzopyrano[4,3-*c*]quinoline-4-carboxylic acid (XI). A mixture of 7.5 g of isatin and 28 g of KOH in 70 ml of 50% aqueous dioxane was stirred for 20 min, then to the mixture was added 7.40 g of *N-tert*-butoxycarbonyl-1,2,3,4-tetrahydroquinolin-4-one (IV) in 20 ml of the same solvent, and the reaction mixture was refluxed for 12 h. 200 ml of water was added, and aqueous solution was acidified with concentrated hydrochloric acid (~ 34 ml) to pH 2–3, extracted with ethyl acetate (5×150 ml), and the extract was dried over anhydrous sodium sulfate. After distilling off the solvent in vacuo the residue was purified by chromatography on silica gel, eluting the title substance with methanol. 3.65 g (27%) of compound XI was isolated. Similarly were synthesized compounds XIII–XVI as mixtures of isomers.

Scheme 5.



Methyl cinchoninates (XVII–XXI). To a solution of 5 mmol of an acid VIII–XII in 15 ml of methanol was added with stirring an ether solution of diazomethane prepared from 1.3 g of *N*-nitrosomethylurea as described in [23]. Nitrogen evolved. The mixture was stirred for 1 h (TLC monitoring), the excess diazomethane was quenched by adding acetic acid, then the solvent was evaporated in a vacuum, the residue was dissolved in ethyl acetate–hexane (2:1) mixture and subjected to chromatography on silica gel, affording respective compounds XVII–XXI. The data on these compounds are listed in Tables 1 and 2.

1-*tert*-Butoxycarbonylpiperidino[4,3-*c*]quinoline-4-carboxamide (XXII). To a mixture of 3.28 g of acid VIII, 5.32 g of BOF in 30 ml of dimethyl sulfoxide (DMSO) was added 1.6 ml of triethylamine, and the mixture was stirred for 1 h at 50°C. Then 3.5 g of ammonium carbonate was added, and the reaction mixture was stirred at room temperature for 50 h. The mixture was poured into 200 ml of water, extracted with ethyl acetate (3×100 ml), washed twice with water, and dried over anhydrous sodium sulfate. After distilling the solvent off in vacuo, the residue was crystallized from ethanol. 1.84 g (56%) of compound

XXII was obtained. Similarly were synthesized amides XXIII–XXVII, their characteristics are listed in Tables 1 and 2. For the synthesis of tertiary amides XXV–XXVII were used *N*-methyl-*N*-methoxyamine and equimolar amount of triethylamine as an acceptor of HCl.

Cinchoninic acids hydrazides (XXVIII–XXX). A mixture of 3 mmol of methyl ester XVII, XVIII, or XXI and 1 ml of hydrazine hydrate in 5 ml of ethanol was heated at reflux with stirring for 2 h (TLC monitoring). The solvent was then removed in vacuo, 15 ml of water was added, and the mixture was kept in a refrigerator at 6–7°C for 10 h. The precipitate of compound XXVIII–XXX, respectively, was filtered off, washed with water, and crystallized from ethanol.

Benzaldehyde hydrazones with cinchoninic acids hydrazides (XXXI–XXXIII). A mixture of 2 mmol of a hydrazide XXVIII–XXX, 0.22 g of freshly distilled benzaldehyde, and 0.2 g of molecular sieve 4A (8–12 mesh) in 5 ml of anhydrous ethanol was refluxed with stirring for 4 h (TLC monitoring), then cooled, filtered, the solvent was distilled off in a vacuum and the residue was crystallized from ethyl acetate–hexane (3:1) to give respective compound XXXI–XXXIII.

Methyl piperidino[4,3-*c*]quinolin-4-carboxylate dihydrochloride (XXXIV). To a solution of 3.42 g of methyl ester **XVII** in 15 ml of anhydrous methanol was added 30 ml of saturated solution of HCl in dioxane, the mixture was stirred for 15 h at room temperature and then for 2 h at 50°C. The solvent was removed in a vacuum, the residue was dissolved in a minimum amount of isopropanol at heating, the solution was cooled, 50 ml of anhydrous diethyl ether was added, and the mixture was left for 15 h in a refrigerator at 6–7°C. The precipitate formed was filtered off, washed with 20 ml of ether, and dried in a vacuum over anhydrous CaCl₂. 3.11 g (99%) of compound **XXXIV** was isolated. Similarly were synthesized compounds **XXXV–XXXVIII**, their characteristics are listed in Tables 1 and 2.

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