*Chemistry of Heterocyclic Compounds, Vol. 46, No. 11, February, 2011 (Russian Original Vol. 46, No. 11, November, 2010)*

# 4-HYDROXY-2-QUINOLONES. 192.* RELATIONSHIP OF STRUCTURE AND ANALGESIC ACTIVITY OF 4-AMINO-2-OXO-1,2-DIHYDROQUINOLINE-3-CARBOXYLIC ACIDS AND THEIR DERIVATIVES

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*Some 4-N-R-2-Oxo-1,2-dihydroquinoline-3-carboxylic acids and their derivatives were synthesized as close structural analogs of the highly-active analgesic 4-benzylamino-2-oxo-1,2-dihydroquinoline-carboxylic acid. Pharmacological testing showed that manifestation of an analgesic effect depends on the presence of a carboxylic group and benzyl fragment in these molecules.*

**Keywords**: 4-N-R-2-oxo-1,2-dihydroquinoline-3-carboxylic acids, analgesic activity, X-ray diffraction crystallographic structural analysis.

A study of the pharmacological properties of 4-R-2-oxo-1,2-dihydroquinoline-3-carboxylic acids has shown that such compounds may be effective analgesics [2]. The 4-amino derivatives have attracted special attention not only in light of their strong pain-relief activity but also due to their extremely weak acidic properties. Many non-narcotic analgesics are such strong acids that even their salts can cause ulcers and, thus, have many contra-indications for use [3]. There is no basis for such a side effect in case of 4-amino derivatives, at least, in such pronounced form. For comparison, the p$K_a$ value of the carboxylic group for 4-benzylamino-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (**1**) is more than 14, while the corresponding value for one of the most powerful non-narcotic analgesics, Ketorolac is only $3.49 \pm 0.02$ [4]. If we also consider its pronounced biological activity, 4-benzylaminoquinoline **1** holds clear interest as an intermediate leader structure in the search for improved analgesics. We have synthesized a series of close analogs of this compound and carried out pharmacological testing to clarify the structural fragments most affecting the analgesic properties.

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* Communication 191, see [1].

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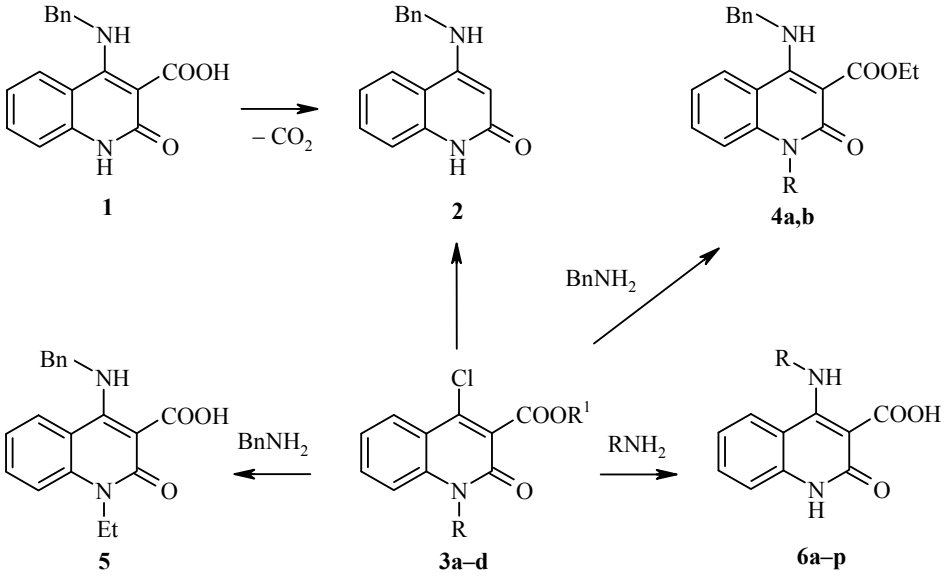
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1690-1701, November, 2010. Original article submitted October 28, 2009.

The first representative of the modified derivatives was 4-(benzylamino)quinolin-2-one (**2**), which is readily obtained by the decarboxylation of initial structure **1** or by the reaction of 4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (**3a**) with benzylamine in high-boiling solvents [5]. The removal of the carboxylic group from the molecule leads to a significant drop in analgesic activity, namely, the capacity to raise the pain sensitivity threshold is reduced by a factor of 3 in comparison with starting acid **1** (see Table 1). Esterification of the carboxylic group (ethyl ester **4a**), N(1)-ethylation of the quinolone system (acid **5**), and esterification with concurrent N(1)-alkylation (N(1)-propyl-substituted ester **4b**) all lead to similar results. This finding is a convincing evidence for the extremely important role of the carboxylic group in producing the biological effect. The introduction of N(1)-alkyl substituents, judging from the examples studied, is undesirable although, on the whole, their effect is not as straightforward and, in principle, may be the subject for further research.




**3 a** R = $R^1$ = H, **b** R = H, $R^1$ = Et, **c** R = Pr, $R^1$ = Et, **d** R = Et, $R^1$ = H;
**4 a** R = H, **b** R = Pr; **6 a** R = Ph, **b** R = $Ph(CH_2)_2$, **c** R = $Ph(CH_2)_3$, **d** R = (±)-MeCH(Ph),
**e** R = *S*(+)-MeCH(Ph), **f** R = *R*(–)-MeCH(Ph), **g** R = 4-$FC_6H_4CH_2$, **h** R = 2-$ClC_6H_4CH_2$,
**i** R = 4-$ClC_6H_4CH_2$, **j** R = 4-$MeC_6H_4CH_2$, **k** R = 2-$MeOC_6H_4CH_2$, **l** R = 4-$MeOC_6H_4CH_2$,
**m** R = 3,4-$(MeO)_2C_6H_3CH_2$, **n** R = piperonyl, **o** R = *S*(+)-$MeCHC_6H_4OMe$-4,
**p** R = *R*(–)-$MeCHC_6H_4OMe$-4

Hence, all our subsequent efforts in the chemical modification of 4-benzylamino-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (**1**) were directed toward introducing changes exclusively in the benzyl part of the molecule. The synthesis of the 4-N-R-substituted quinoline-3-carboxylic acids **6a-t** was carried out by a single scheme through the reaction of the corresponding primary amines with 4-chloro-2-oxo-1,2-dihydroquinoline-2-carboxylic acid (**3a**) in ethanol at reflux, i.e., under conditions excluding the possibility of decarboxylation.

The structure of the compounds obtained was confirmed by $^1$H NMR spectroscopy. The presence of all the proton-containing functional groups was reliably determined (Table 2). Only the question concerning the three-dimensional structure of acids **6e**,**f** and **6o**,**p** synthesized using optically active 1-arylethylamines remained open.

TABLE 1. Characteristics of Synthesized Compounds

| Compound* | Empirical formula | Found, % / Calculated, % | | | mp, °C (ethanol) | Yield, % | A. a.*[2] |
|---|---|---|---|---|---|---|---|
| | | C | H | N | | | |
| **2** | $C_{16}H_{14}N_2O$ | 76.64 / 76.78 | 5.53 / 5.64 | 11.13 / 11.19 | 250-252 | 92 | 24.8 |
| **4a** | $C_{19}H_{18}N_2O_3$ | 70.65 / 70.79 | 5.74 / 5.63 | 8.78 / 8.69 | 140-142 | 90 | 18.0 |
| **4b** | $C_{22}H_{24}N_2O_3$ | 72.62 / 72.51 | 6.58 / 6.64 | 7.52 / 7.69 | 121-122 | 72 | 28.8 |
| **5** | $C_{19}H_{18}N_2O_3$ | 70.68 / 70.79 | 5.56 / 5.63 | 8.57 / 8.69 | 104-106 (dec.) | 93 | 7.6 |
| **6a** | $C_{16}H_{12}N_2O_3$ | 68.68 / 68.57 | 4.40 / 4.32 | 10.08 / 9.99 | 243-245 (dec.) | 95 | 26.0 |
| **6b** | $C_{18}H_{16}N_2O_3$ | 70.23 / 70.12 | 5.31 / 5.23 | 8.97 / 9.09 | 209-211 (dec.) | 90 | 35.2 |
| **6c** | $C_{19}H_{18}N_2O_3$ | 70.90 / 70.79 | 5.75 / 5.63 | 8.83 / 8.69 | 194-196 (dec.) | 84 | 7.5 |
| **6d** | $C_{18}H_{16}N_2O_3$ | 70.03 / 70.12 | 5.17 / 5.23 | 9.16 / 9.09 | 225-227 (dec.) | 75 | 40.1 |
| **6e** | $C_{18}H_{16}N_2O_3$ | 70.05 / 70.12 | 5.15 / 5.23 | 8.95 / 9.09 | 230-232 (dec.) | 78 | 2.2 |
| **6f** | $C_{18}H_{16}N_2O_3$ | 69.98 / 70.12 | 5.14 / 5.23 | 9.13 / 9.09 | 230-232 (dec.) | 74 | 2.0 |
| **6g** | $C_{17}H_{13}FN_2O_3$ | 65.47 / 65.38 | 4.33 / 4.20 | 9.09 / 8.97 | 227-229 (dec.) | 93 | 35.0 |
| **6h** | $C_{17}H_{13}ClN_2O_3$ | 62.20 / 62.11 | 4.12 / 3.99 | 8.66 / 8.52 | 238-240 (dec.) | 91 | 42.7 |
| **6i** | $C_{17}H_{13}ClN_2O_3$ | 62.22 / 62.11 | 4.07 / 3.99 | 8.43 / 8.52 | 240-242 (dec.) | 96 | 18.1 |
| **6j** | $C_{18}H_{16}N_2O_3$ | 70.25 / 70.12 | 5.34 / 5.23 | 8.97 / 9.09 | 229-231 (dec.) | 89 | 20.5 |
| **6k** | $C_{18}H_{16}N_2O_4$ | 66.54 / 66.66 | 4.84 / 4.97 | 8.55 / 8.64 | 222-224 (dec.) | 93 | 5.8 |
| **6l** | $C_{18}H_{16}N_2O_4$ | 66.53 / 66.66 | 4.85 / 4.97 | 8.57 / 8.64 | 218-220 (dec.) | 95 | 11.9 |
| **6m** | $C_{19}H_{18}N_2O_5$ | 64.31 / 64.40 | 5.20 / 5.12 | 8.02 / 7.91 | 215-217 (dec.) | 88 | 28.3 |
| **6n** | $C_{18}H_{14}N_2O_5$ | 63.79 / 63.90 | 4.06 / 4.17 | 8.19 / 8.28 | 207-209 (dec.) | 92 | 32.2 |
| **6o** | $C_{19}H_{18}N_2O_4$ | 67.34 / 67.45 | 5.27 / 5.36 | 8.17 / 8.28 | 166-168 (dec.) | 76 | 46.1 |
| **6p** | $C_{19}H_{18}N_2O_4$ | 67.31 / 67.45 | 5.22 / 5.36 | 8.14 / 8.28 | 166-168 (dec.) | 74 | 31.6 |
| **1** | — | — | — | — | — | — | 75.4 [2] |
| | Diclofenac | — | — | — | — | — | 34.1 |
| | Keterolac | — | — | — | — | — | 46.4 |

* $[\alpha]^{20}_D$ ($c$ = 3, DMF): +190.7° (**6e**); -190.7° (**6f**); +157.4° (**6o**); -157.4° (**6p**).
*[2] Analgesic activity (increase of the pain threshold), %.

We attempted to obtain an unequivocal answer to this question by X-ray analysis and initially studied 4-(1-phenylethylamino)quinoline-3-carboxylic acid 6f obtained from R-1-phenylethylamine (see Fig. 1 and Tables 3 and 4). The bicyclic quinolone system, atom N(2), carbonyl group, and carboxylic group in this compound lie in the same plane within ±0.02 Å due to the formation of two strong intramolecular hydrogen bonds N(2)–H(2N)···O(2) (H···O, 1.81 Å; N–H···O, 146°) and O(3)–H(3O)···O(1) (H···O, 1.43 Å; O–H···O, 148°). The formation of these hydrogen bonds accounts for the significant redistribution of electron density in the quinolone fragment indicated by lengthening of the O(1)–C(9) (1.273(1) Å) and O(2)-C(10) bonds (1.234(2) Å) in comparison with the mean value (1.210 Å [6]), lengthening of the C(7)-C(8) bond (1.410(2) Å,

mean value 1.326 Å), and contraction of the O(3)-C(10) (1.316(1) Å, mean value 1.362 Å) and C(8)-C(9) bonds (1.420(2) Å, mean value 1.455 Å). The substituent on the amino group is (1.273(1) Å) and O(2)–C(10) bonds (1.234(2) Å) in comparison with the mean value (1.210 Å [6]), lengthening in *syn*-periplanar conformation

TABLE 2. $^1$H NMR Spectra of 4-N-R-2-Oxo-1,2-dihydroquinolines **4-6**

| Com-pound | Chemical shifts, δ, ppm (*J*, Hz) |
|---|---|
| **4a** | 11.13 (1H, s, NH); 8.13 (1H, d, *J* = 8.2, H-5); 7.54-7.10 (9H, m, H-6,7,8 + NHCH$_2$C$_6$H$_5$); 4.46 (2H, d, *J* = 6.1, NCH$_2$); 3.91 (2H, q, *J* = 7.0, COOCH$_2$); 0.97 (3H, t, *J* = 7.0, CH$_3$) |
| **4b** | 8.22 (1H, d, *J* = 8.3, H-5); 7.64 (1H, t, *J* = 7.7, H-7); 7.40-7.05 (8H, m, H-6,8 + NHCH$_2$C$_6$H$_5$); 4.47 (2H, d, *J* = 6.2, NHCH$_2$); 4.07 (2H, t, *J* = 7.2, NCH$_2$CH$_2$Me); 3.93 (2H, q, *J* = 7.1, COOCH$_2$); 1.55 (2H, m, NCH$_2$CH$_2$Me); 1.11 (3H, t, *J* = 7.1, OCH$_2$CH$_3$); 0.96 (3H, t, *J* = 6.9, NCH$_2$CH$_2$CH$_3$) |
| **5** | 16.57 (1H, s, COOH); 11.26 (1H, t, *J* = 4.8, NH); 8.29 (1H, d, *J* = 8.1, H-5); 7.85-7.28 (8H, m, H-6,7,8 + CH$_2$C$_6$H$_5$); 5.05 (2H, d, *J* = 5.3, NHCH$_2$C$_6$H$_5$); 4.29 (2H, q, *J* = 7.1, NCH$_2$Me); 1.23 (3H, t, *J* = 7.2, NCH$_2$CH$_3$) |
| **6a** | 16.71 (1H, s, COOH); 12.42 (1H, s, NHPh); 12.21 (1H, s, NH); 7.58 (1H, t, *J* = 7.8, H-7); 7.45-7.20 (7H, m, H-5,6,8 + H-2',3',5',6'); 6.93 (1H, t, *J* = 7.7, H-4') |
| **6b** | 16.58 (1H, s, COOH); 11.92 (1H, s, NH); 11.15 (1H, t, *J* = 4.2, NHCH$_2$); 8.23 (1H, d, *J* = 8.4, H-5); 7.66 (1H, t, *J* = 7.6, H-7); 7.40-7.15 (7H, m, H-6,8 + CH$_2$C$_6$H$_5$); 4.12 (2H, q, *J* = 4.8, NCH$_2$CH$_2$Ph); 2.99 (2H, t, *J* = 6.9, NCH$_2$CH$_2$Ph) |
| **6c** | 16.67 (1H, s, COOH); 11.86 (1H, s, NH); 11.22 (1H, t, *J* = 4.2, NHCH$_2$); 8.14 (1H, d, *J* = 8.4, H-5); 7.65 (1H, t, *J* = 7.6, H-7); 7.38 (1H, d, *J* = 8.4, H-8); 7.30-7.12 (6H, m, H-6 + CH$_2$C$_6$H$_5$); 3.85 (2H, q, *J* = 5.1, NCH$_2$); 2.72 (2H, t, *J* = 7.6, NCH$_2$CH$_2$CH$_2$Ph); 1.99 (2H, q, *J* = 7.2, NCH$_2$CH$_2$CH$_2$Ph) |
| **6d–f** | 16.78 (1H, s, COOH); 12.01 (1H, s, NH); 11.63 (1H, d, *J* = 7.5, NHCH); 7.97 (1H, d, *J* = 8.5, H-5); 7.58 (1H, t, *J* = 7.8, H-7); 7.43-7.19 (6H, m, H-8 + CHC$_6$H$_5$); 7.07 (1H, t, *J* = 7.7, H-6); 5.54 (1H, q, *J* = 6.8, NHCH); 1.59 (3H, d, *J* = 6.8, CH$_3$) |
| **6g** | 16.65 (1H, s, COOH); 12.06 (1H, s, NH); 11.35 (1H, t, *J* = 4.9, NHCH$_2$); 8.24 (1H, d, *J* = 8.6, H-5); 7.67 (1H, t, *J* = 7.8, H-7); 7.55-7.17 (6H, m, H-6,8 + CH$_2$Ar); 5.06 (2H, d, *J* = 5.2, NHCH$_2$) |
| **6h** | 16.59 (1H, s, COOH); 12.01 (1H, s, NH); 11.20 (1H, t, *J* = 4.9, NHCH$_2$); 8.14 (1H, d, *J* = 8.6, H-5); 7.68 (1H, t, *J* = 7.6, H-7); 7.62-7.19 (6H, m, H-6,8 +CH$_2$Ar); 5.12 (2H, d, *J* = 5.3, NHCH$_2$) |
| **6i** | 16.66 (1H, s, COOH); 11.77 (1H, s, NH); 11.35 (1H, t, *J* = 5.0, NHCH$_2$); 8.20 (1H, d, *J* = 8.6, H-5); 7.67 (1H, t, *J* = 7.8, H-7); 7.49-7.36 (5H, m, H-8 + CH$_2$Ar); 7.23 (1H, t, *J* = 7.7, H-6); 5.09 (2H, d, *J* = 5.5, NHCH$_2$) |
| **6j** | 16.64 (1H, s, COOH); 11.93 (1H, s, NH); 11.34 (1H, t, *J* = 4.8, NHCH$_2$); 8.26 (1H, d, *J* = 8.6, H-5); 7.66 (1H, t, *J* = 7.7, H-7); 7.39 (1H, d, *J* = 8.1, H-8); 7.31 (2H, d, *J* = 8.1, H-2',6'); 7.20 (3H, m, H-6 + H-3',5'); 5.04 (2H, d, *J* = 5.1, NHCH$_2$); 2.29 (3H, s, CH$_3$) |
| **6k** | 16.57 (1H, s, COOH); 11.91 (1H, s, NH); 11.21 (1H, t, *J* = 5.1, NHCH$_2$); 8.21 (1H, d, *J* = 8.4, H-5); 7.67 (1H, t, *J* = 7.9, H-7); 7.44-6.89 (6H, m, H-6,8,3',4',5',6'); 4.98 (2H, d, *J* = 5.4, NHCH$_2$); 3.79 (3H, s, OCH$_3$) |
| **6l** | 16.63 (1H, s, COOH); 11.98 (1H, s, NH); 11.30 (1H, t, *J* = 4.6, NHCH$_2$); 8.28 (1H, d, *J* = 8.6, H-5); 7.67 (1H, t, *J* = 7.8, H-7); 7.42-7.31 (3H, m, H-8,2',6'); 7.24 (1H, t, *J* = 7.8, H-6); 6.95 (2H, d, *J* = 8.6, H-3',5'); 5.00 (2H, d, *J* = 5.1, NHCH$_2$); 3.74 (3H, s, OCH$_3$) |
| **6m** | 16.64 (1H, s, COOH); 11.92 (1H, s, NH); 11.33 (1H, t, *J* = 4.7, NHCH$_2$); 8.27 (1H, d, *J* = 8.3, H-5); 7.67 (1H, t, *J* = 7.7, H-7); 7.40 (1H, d, *J* = 8.3, H-8); 7.25 (1H, t, *J* = 7.7, H-6); 7.05 (1H, s, H-2'); 6.96 (2H, s, H-5',6'); 5.01 (2H, d, *J* = 5.0, NHCH$_2$); 3.74 (3H, s, OCH$_3$); 3.72 (3H, s, OCH$_3$) |
| **6n** | 16.65 (1H, s, COOH); 12.04 (1H, s, NH); 11.28 (1H, t, *J* = 4.5, NHCH$_2$); 8.25 (1H, d, *J* = 8.2, H-5); 7.68 (1H, t, *J* = 7.8, H-7); 7.39 (1H, d, *J* = 8.2, H-8); 7.25 (1H, t, *J* = 7.6, H-6); 7.00 (1H, s, H-2'); 6.92 (2H, s, H-5',6'); 6.02 (2H, s, OCH$_2$O); 4.98 (2H, d, *J* = 4.6, NHCH$_2$) |
| **6o**,**p** | 16.75 (1H, s, COOH); 11.95 (1H, s, NH); 11.57 (1H, d, *J* = 7.6, NHCH); 8.01 (1H, d, *J* = 8.2, H-5); 7.59 (1H, t, *J* = 7.6, H-7); 7.38-7.27 (3H, m, H-8 + H-3',5'); 7.10 (1H, t, *J* = 7.8, H-6); 6.91 (2H, d, *J* = 8.7, H-2',6'); 5.49 (1H, q, *J* = 7.0, NHCH); 3.70 (3H, s, OCH$_3$); 1.57 (3H, d, *J* = 7.0, CHCH$_3$) |

relative to the C(6)–C(7) bond (the C(11)–N(2)–C(7)–C(6) torsion angle is -19.7(2)°) and rotated such that the methyl group has *–ac*-orientation relative to the C(7)–N(2) bond (the C(7)–N(2)–C(11)–C(12) torsion angle is -143.0(2)°), while the phenyl substituent is almost perpendicular to the C(7)–N(2) bond and somewhat twisted relative to the N(2)–C(11) bond (the C(7)–N(2)–C(11)–C(13) torsion angle is 94.6(2)° and the N(2)–C(11)–C(13)–C(14) torsion angle is 10.7(2)°). This position of the amino group substituent leads to strong repulsion between it and the aromatic ring of the quinolone fragment (short contacts H(5)···C(11), 2.46 Å (sum of the van der Waals radii [7] 2.87 Å), H(5)···H(11), 2.07 Å (2.34 Å), H(5)···C(13), 2.42 Å (2.87 Å), H(11)···C(5), 2.65 Å (2.87 Å)). We may assume that the steric strain is partially compensated by some out-of-plane deformation of the aromatic fragment of the quinolone fragment (the torsion angle C(2)–C(1)–C(6)–C(5) is 4.1(2)°), distortion of the C(5)–C(6)–C(7)–N(2) (-6.1(2)°) and C(6)–C(7)–C(8)–C(9) torsion angles (4.0(2)°), as well as slight pyramidalization of the amino group nitrogen atom (the sum of the valence angles centered at atom N(2) is 358.7°). In previous work [8], we have shown that the benzene ring is conformationally flexible and may be deformed by external forces such as steric strain. We cannot exclude that this accounts for the degeneration of the $^{1}$H NMR signals for H-5' and H-6' protons in the 3,4-dimethoxy-benzyl (**6m**) and piperonyl (**6o**) derivatives into one singlet with intensity 2H instead of two theoretical doublets (Table 2).

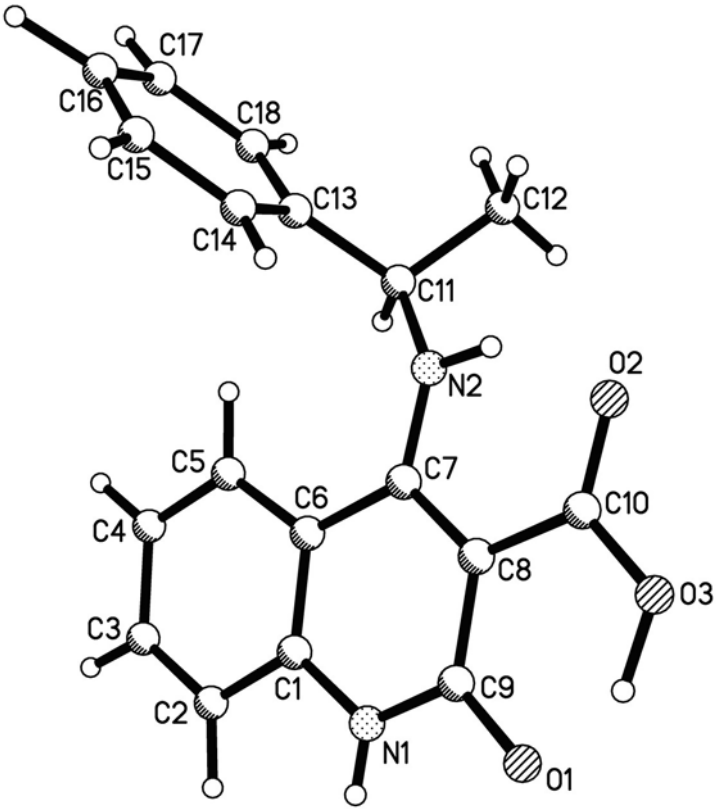



Fig. 1. Molecular structure of acid **6f** with numbering of the atoms.

A series of shortened contacts was found for this sample: H(2)···H(1N), 2.23 Å (sum of van der Waals radii 2.34 Å); H(12a)···H(2N), 2.24 Å (2.34 Å); H(12b)···C(18), 2.78 Å (2.87 Å); H(14)···N(2), 2.51 Å (2.67 Å).

The crystal of acid **6f** features stacks along the crystallographic direction (1 0 0), in which the distance between the quinolone aromatic ring and the π-system of the carbonyl and carboxylic groups of adjacent

TABLE 3. Bond Lengths (*l*) in the Structure of Acid **6f**

| Bond | *l*, Å | Bond | *l*, Å |
|---|---|---|---|
| O(1)–C(9) | 1.273(1) | O(2)–C(10) | 1.234(2) |
| O(3)–C(10) | 1.316(1) | N(1)–C(9) | 1.343(2) |
| N(1)–C(1) | 1.380(2) | N(2)–C(7) | 1.338(2) |
| N(2)–C(11) | 1.457(2) | C(1)–C(6) | 1.396(2) |
| C(1)–C(2) | 1.401(2) | C(2)–C(3) | 1.355(2) |
| C(3)–C(4) | 1.381(2) | C(4)–C(5) | 1.378(2) |
| C(5)–C(6) | 1.402(2) | C(6)–C(7) | 1.462(2) |
| C(7)–C(8) | 1.410(2) | C(8)–C(9) | 1.420(2) |
| C(8)–C(10) | 1.472(2) | C(11)–C(13) | 1.511(2) |
| C(11)–C(12) | 1.531(2) | C(13)–C(14) | 1.360(2) |
| C(13)–C(18) | 1.373(2) | C(14)–C(15) | 1.410(2) |
| C(15)–C(16) | 1.350(2) | C(16)–C(17) | 1.349(2) |
| C(17)–C(18) | 1.383(2) | | |

TABLE 4. Valence Angles (ω) in the Structure of Acid **6f**

| Valence angle | ω, deg | Valence angle | ω, deg |
|---|---|---|---|
| C(9)–N(1)–C(1) | 123.8(1) | C(7)–N(2)–C(11) | 133.3(1) |
| N(1)–C(1)–C(6) | 120.2(1) | N(1)–C(1)–C(2) | 118.4(1) |
| C(6)–C(1)–C(2) | 121.4(1) | C(3)–C(2)–C(1) | 119.8(2) |
| C(2)–C(3)–C(4) | 120.7(2) | C(5)–C(4)–C(3) | 119.6(2) |
| C(4)–C(5)–C(6) | 122.0(2) | C(1)–C(6)–C(5) | 116.5(1) |
| C(1)–C(6)–C(7) | 118.2(1) | C(5)–C(6)–C(7) | 125.3(1) |
| N(2)–C(7)–C(8) | 118.2(1) | N(2)–C(7)–C(6) | 123.5(1) |
| C(8)–C(7)–C(6) | 118.4(1) | C(7)–C(8)–C(9) | 120.6(1) |
| C(7)–C(8)–C(10) | 122.5(1) | C(9)–C(8)–C(10) | 116.9(1) |
| O(1)–C(9)–N(1) | 117.4(1) | O(1)–C(9)–C(8) | 123.9(1) |
| N(1)–C(9)–C(8) | 118.7(1) | O(2)–C(10)–O(3) | 119.6(1) |
| O(2)–C(10)–C(8) | 123.7(1) | O(3)–C(10)–C(8) | 116.8(1) |
| N(2)–C(11)–C(13) | 114.4(1) | N(2)–C(11)–C(12) | 106.2(1) |
| C(13)–C(11)–C(12) | 110.7(1) | C(14)–C(13)–C(18) | 117.5(1) |
| C(14)–C(13)–C(11) | 123.2(1) | C(18)–C(13)–C(11) | 119.4(1) |
| C(13)–C(14)–C(15) | 120.8(2) | C(16)–C(15)–C(14) | 120.0(2) |
| C(17)–C(16)–C(15) | 119.8(2) | C(16)–C(17)–C(18) | 120.1(2) |
| C(13)–C(18)–C(17) | 121.7(2) | | |

molecules is 3.37 Å, indicating a stacking interaction between these moieties. The molecules of adjacent stacks are connected by hydrogen bonds N(1)–H(1N)···O(2)' [(-*x*, 0.5 + *y*, 1-*z*), H···O, 2.15 Å, N–H···O, 148°] and C(16)–H(16)···C(9)' [*x*, *y*, 1+*z*), H···π, 2.84 Å, C–H···π, 152°].

Absolutely identical crystallographic parameters were found for the optical antipode of acid **6f**, i.e., 4-(1-phenylethylamino)quinoline-3-carboxylic acid **6e** obtained from *S*-1-phenylethylamine. Nevertheless, in none of these examples, the chiral center configuration unfortunately failed to be determine reliably. We can only confirm that each of the crystals studied indeed contains only one of the enantiomers since both compounds give crystals with the noncentrosymmetric $P2_1$ space group. The true configuration of a chiral center is determined using the Flack parameter. The absolute configuration is considered true if the Flack parameter is equal to zero but requires inversion if this parameter is equal to 1 [9, 10]. However, since crystals of acids **6f** and **6e** lack heavy atoms, there is no anomalous X-ray scattering permitting the correct calculation of the Flack parameter. The value of this parameter for these compounds is -0.4(6), which is a meaningless value.

We have encountered a similar situation in an attempt to use X-ray diffraction structural analysis to determine the absolute configuration of 1-phenylethylamides of 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids [11]. In this work [12], we were able to obtain convincing proof that neither racemization nor inversion of configuration occurs upon the amidation of the ethyl esters of the corresponding quinoline-3-carboxylic acids with optically pure 1-phenylethylamines. In other words, we have additional experimental proof that the long-known considerable optical stability of 1-arylethylamines in reactions are not affecting the asymmetric sites [13]. On the basis of these results and taking into account the identical melting points, completely identical $^{1}$H NMR spectra, and furthermore, the same specific rotations differing only in sign (this finding in itself serves as rather reliable proof for the optical purity of the compounds studied [13]), we may conclude that acids **6e**,**f**, similar to the enantiomer pair **6o**,**p**, retain the configuration of the starting 1-arylethylamines.

Our chemical modification of the benzyl fragment of acid **1** may be divided into three directions. The first two directions affect separately the methylene unit or phenyl ring, respectively. The third direction affects both these groups concurrently. The pharmacological testing showed that removal of the methylene bridge connecting the secondary amino group and aromatic ring (4-N-phenyl derivative **6a**) has the same effect on the analgesic properties as decarboxylation discussed above, i.e., leads to a drop in activity by a factor of about 3 (Table 1). The replacement of the methylene group by ethylene and, especially, propylene chain also should be considered unsuccessful. While the analgesic effect in going to 2-phenylethyl derivative **6b** drops by a factor of 2, which nevertheless remains on the level of Diclofenac, there is almost no analgesic effect found for the 3-phenylpropyl derivative **6c**.

Methylation of the methylene unit in acid **1** led to somewhat unusual results. One asymmetric carbon atom appears as the result of this transformation. Thus, the final product may be seen as racemic mixture **6d**, or one of the enantiomers with *S*- or *R*-configuration of the chiral center (**6e** or **6f**, respectively). Depending on the three-dimensional structure of the biological target and another of other factors, enantiomers can display identical pharmacological properties or differ sharply, sometimes giving completely opposite effects. Hence, the retention of activity on the former level usually observed in practice and the significant drop or even complete loss in the latter would appear to be logical consequences. In this regard, the rather high analgesic activity of racemic 2-oxo-1-phenylethyl-1,2-dihydroquinoline-3-carboxylic acid **6d** despite the lack of biological activity of pure enantiomers **6e** and **6f** would appear somewhat unexpected. The water-insoluble tested compounds were introduced into the experimental animals as aqueous suspensions. Thus, it is not excluded that the observed effect results from differences in the crystal forms. Grounds for this proposal exist. For example, in contrast to optical antipodes **6e** and **6f**, racemic acid **6d** cannot crystallize in a noncentrosymmetric space group. However, the final conclusion in this matter can be drawn only after special additional experiments. Presently, we can only note that there have been so many examples of a significant effect of the crystal structure of drugs on their pharmacological action that polymorphism of pharmaceutical compounds has grown from a curious phenomenon into an extremely important subject for investigation relative to its scientific aspects and industrial applications [14].

The second direction in the chemical modification of the leading structure is represented by 4-benzylamino-2-oxo-1,2-dihydroquinoline-3-carboxylic acids **6g-n** with substituents in the aromatic ring of the benzyl fragment. Unfortunately, in all cases, without regard to the substituents introduced and their position in the ring, a drop in analgesic activity is consistently observed (Table 1). 2-Chlorobenzyl derivative **6h**, which is only slightly inferior in its specific activity relative to ketorolac, is perhaps the only compound of this group deserving further attention.

Finally, the third group with modifications of the 4-N-benzyl substituent of acid **1** featuring changes both in the methylene unit and aromatic ring is represented by only two compounds, optically active 4-[1-ethyl(4-methoxyphenyl)amino]-2-oxo-1,2-dihydroquinoline-3-carboxylic acids **6o** and **6p**. Here, we clearly

discern the effect of the spatial configuration of the asymmetric carbon atom on the strength of the analgesic effect: *S*-enantiomer **6o** is much more active than its *R*-antipode **6p**. It is also interesting to note that the separately-introduced methyl group into the methylene unit (acid **6e**) or 4-methoxyl group into the aromatic ring (acid **6l**) lead to complete loss of analgesic properties. However, the effect of the same substituents when introduced concurrently is not as clear-cut. In particular, the activity of acid **6o** is on the level of Ketorolac, which is one of the most powerful non-narcotic analgesics.

Therefore, our results indicate that the carboxylic group in the structure of 4-benzylamino-2-oxo-1,2-dihydroquinoline-3-carboxylic acids undoubtedly plays the key role in binding to receptors. The benzyl group is another important structural fragment providing a tighter interaction with the biological target. On the other hand, the role of the 1-N-alkyl substituents is not as unequivocal and requires careful investigation. The importance of the benzene part of the quinolone system and the secondary amino group at C-4 still remains completely unclear.

## EXPERIMENTAL

The $^1$H NMR spectra were taken on a Varian Mercury-VX-200 spectrometer at 200 MHz in DMSO-$d_6$ as the solvent with TMS as the internal standard. The specific rotations of acids **6e, 6f, 6o,** and **6p** were determined on a Polamat A polarimeter. These compounds were synthesized using commercial samples of *S*(-)- and *R*(+)-1-phenyl- and 1-(4-methoxyphenyl)ethylamines with optical purity of at least 99.5 and 99.0%, respectively, supplied by Fluka. The analgesic activity of the resultant 4-N-R-2-oxo-1,2-dihydroquinolines was studied on the standard model of irritation of rectal mucous membrane by an electrical shock [15] described in detail in our previous work [2].

**4-Benzylamino-1H-quinolin-2-one (2).** A solution of 4-benzylamino-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (**1**) (2.94 g, 0.01 mol) in DMF (10 ml) was heated at reflux for 30 min. The reaction mixture was cooled and diluted with cold water. The formed precipitate of quinolone **2** was filtered off, washed with water, and dried. A mixed probe with a sample of 4-benzylaminoquinolin-2-one obtained by the reaction of 4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylic acid with benzylamine in DMF [5] does not give a melting point depression. The $^1$H NMR spectra of the two samples were identical.

**4-N-R-2-Oxo-1,2-dihydroquinoline-3-carboxylic Acids and their Ethyl Esters 4-6 (General Method).** Corresponding amine (0.011 mol) and triethylamine (1.4 ml, 0.01 mol) were added to a solution of corresponding 1-R-4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylic acid or its ethyl ester **3a-d** (0.01 mol) in 20 ml ethanol, heated at reflux for 2-3 h, and then cooled. The resultant 4-N-R-2-oxo-1,2-dihydroquinoline-3-carboxylic acid **5** or **6a-p** was filtered off, washed with water and then ethanol, and dried. In the separation of ethyl esters **4a**,**b**, the reaction mixture was diluted with cold water. The precipitate was filtered off, washed with water, and dried.

**X-ray Diffraction Structural Analysis.** Monoclinic crystals of acid **6f** obtained by recrystallization from ethanol were studied at 20°C. The unit cell parameters are $a = 5.2967(5)$, $b = 12.564(1)$, $c = 11.272(1)$ Å, $\beta = 92.806(8)°$, $V = 749.2(1)$ Å$^3$, $M_r = 308.33$, $Z = 2$, space group $P2_1$, $d_{calc} = 1.367$ g/cm$^3$, $\mu(MoK\alpha) = 0.094$ mm$^{-1}$, $F(000) = 324$. The unit cell parameters and intensities of 8525 reflections (4057 independent reflections, $R_{int} = 0.026$) were measured on an Xcalibur-3 diffractometer using MoK$\alpha$ radiation, CCD detector, graphite monochromator, $\omega$-scanning, $2\theta_{max} = 60°$.

The structure was solved by the direct method using the *SHELXTL* program package [16]. The hydrogen atoms were revealed from the electron density difference map and refined isotropically. The structure was refined anisotropically by the full-matrix method of least squares relative to $F^2$ for the non-hydrogen atoms

to $wR_2 = 0.042$ for 4001 reflections ($R_1 = 0.028$ for 2013 reflections with $F > 4\sigma(F)$, $S = 0.716$). The complete crystallographic data set has been deposited in the Cambridge Crystallographic Data Center (CCDC 756717). The interatomic distances and valence angles are given in Tables 3 and 4, respectively.

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