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# 4-HYDROXY-2-QUINOLONES. 191.* SYNTHESIS, TAUTOMERISM AND BIOLOGICAL ACTIVITY OF BENZIMIDAZOL-2-YLAMIDES OF 1-R-4-HYDROXY-2-OXO-1,2-DIHYDROQUINOLINE-3-CARBOXYLIC ACIDS

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*A series of benzimidazol-2-ylamides of 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids was prepared in a search for biologically active compounds. These compounds exist in the crystal exclusively in the amide form, while in solution amide↔imide tautomerism is observed. The results of a study of the antithyroid and antituberculosis activities of these compounds are given.*

**Keywords**: 2-aminobenzimidazole, 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamides, antithyroid activity, antituberculosis activity, tautomerism.

It has recently been noticed more frequently that many autoimmune and other human diseases such as rheumatoid arthritis [2], lupus [3], Sjögren's syndrome [4], myasthenia [5], kidney disease [6], cancer [7], and tuberculosis [8] are accompanied by hyperfunction of the thyroid gland. Thus, after diagnosis of such diseases, it is strongly recommended to check periodically the thyroid hormone level so that, when necessary, the therapy can be properly modified. Furthermore, the current arsenal of antithyroid drugs available to the physicians is very limited. The present drugs have serious side effects and, as a consequence, many contraindications for practical application [9-15]. For this reason, the search for new safe drugs suitable for treating hyperthyroidotoxicosis holds considerable importance today.

Compounds with high antithyroid activity, low toxicity, and no goiter-inducing effect were discovered in a study of the biological properties of 3-(benzimidazol-2-yl)-4-hydroxy-2-oxo-1,2-dihydroquinolines [16] and then their many structural analogs [17-20]. As a result, a new drug has been developed on the basis of one of them for treating diseases related to overproduction of thyroid hormones [21].

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* Communication 190, see [1].

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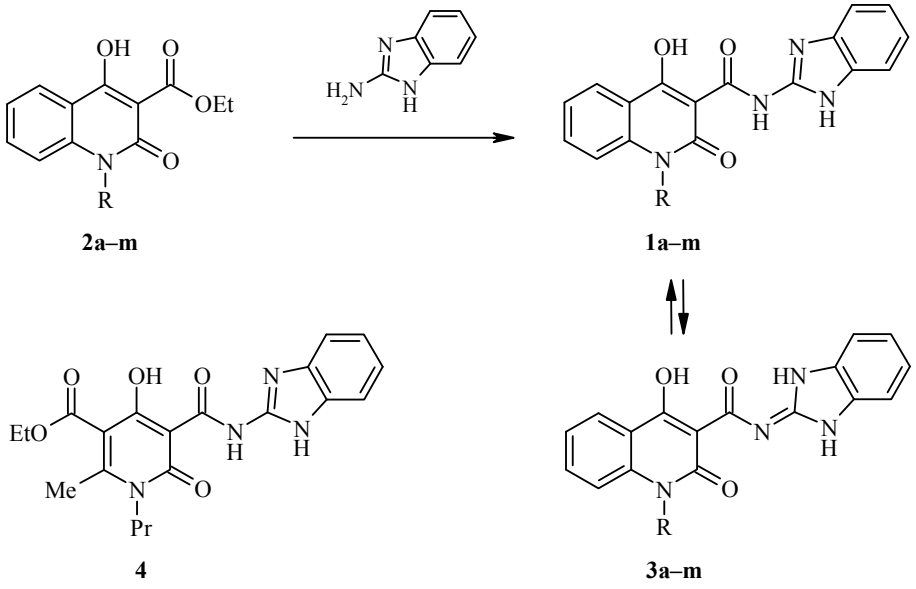
In a continuation of a study in this area, we investigated benzimidazol-2-ylamides of 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids **1a-m**. These compounds differ from the most active product, 3-(benzimidazol-2-yl)-4-oxo-1,2-dihydroquinoline, only in the presence of a carbamide bridge connecting the quinoline and benzimidazole rings. We studied the effect of such structural modification on the physicochemical and biological properties of these compounds.

Benzimidazol-2-ylamides **1a-m** were synthesized by a well-known method involving heating of ethyl esters **2a-m** with 2-aminobenzimidazole [22].




**2a–m** **1a–m**

**4** **3a–m**

**1–3 a** R = H, **b** R = Me, **c** R = Et, **d** R = $CH_2CH{=}CH_2$, **e** R = Pr, **f** R = Bu, **g** R = *i*-Bu, **h** R = $C_5H_{11}$, **i** R = *i*-$C_5H_{11}$, **j** R = $C_6H_{13}$, **k** R = $C_7H_{15}$, **l** R = $C_8H_{17}$, **m** R = $C_9H_{19}$

The obtained hetarylamides **1a-m** (Table 1) are colorless, crystalline compounds with clear melting points, poor solubility in ethanol and water, and good solubility in hot DMSO and DMF at reflux.

We should note the signals for protons H-4 and H-7 of the benzimidazole system in the $^1$H NMR spectra of all the products shown in Table 2. In contrast to protons H-5 and H-6 in the some fragment, which give rise to a well-resolved sextet with coupling constant of about 3.0 Hz typical for benzimidazoles, an almost unresolved broad multiplet with intensity corresponding to 2H is found for protons H-4 and H-7. We have already found such behavior in a study of the $^1$H NMR spectrum of a compound with similar structure, namely, the benzimidazol-2-ylamide of 4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid [23]. This behavior is attributed specifically to the carbamide bridge connecting the two heterocyclic fragments. For comparison, such anomalies are not found in the absence of this bridge [16, 24] or when it is replaced by a methylene or ethylene unit [20].

In light of its specific structure, 2-aminobenzimidazole is a somewhat unusual compound capable of reaction with electrophilic reagents both in the amino and imino forms [25]. Thus, it is entirely justified to expect the 2-N-quinolinoyl derivatives derived from this compound to exist as the amides **1a-m**, imides **3a-m**, or as both these tautomers simultaneously. The broadening of the $^1$H NMR signals of benzimidazole protons H-4 and H-7 indicates not only that these compounds form amide↔imide mixtures in DMSO-$d_6$ but also a slow transition between these tautomeric forms. This hypothesis is supported by a simple experiment. Upon heating solutions of these compounds to 50°C, the rate of proton exchange increases and the initially broad multiplets for benzimidazole protons H-4 and H-7 transform into normal sextets with coupling constant 2.9-3.0 Hz.

TABLE 1. Characteristics of Products **1a-m**

| Compound | Empirical formula | Found, % / Calculated, % | | | mp, °C (DMF) | Yield, % |
|---|---|---|---|---|---|---|
| | | C | H | N | | |
| **1a** | $C_{17}H_{12}N_4O_3$ | 63.88 / 63.75 | 3.90 / 3.78 | 17.39 / 17.49 | 357-359 | 93 |
| **1b** | $C_{18}H_{14}N_4O_3$ | 64.76 / 64.67 | 4.34 / 4.22 | 16.85 / 16.76 | 284-286 | 91 |
| **1c** | $C_{19}H_{16}N_4O_3$ | 65.51 / 65.63 | 4.63 / 4.74 | 16.08 / 16.17 | 251-253 | 87 |
| **1d** | $C_{20}H_{16}N_4O_3$ | 66.66 / 66.75 | 4.48 / 4.60 | 15.55 / 15.44 | 267-269 | 90 |
| **1e** | $C_{20}H_{18}N_4O_3$ | 66.29 / 66.18 | 5.01 / 4.93 | 15.46 / 15.59 | 262-264 | 92 |
| **1f** | $C_{21}H_{20}N_4O_3$ | 67.01 / 66.90 | 5.36 / 5.27 | 14.88 / 14.98 | 245-247 | 85 |
| **1g** | $C_{21}H_{20}N_4O_3$ | 67.01 / 66.88 | 5.36 / 5.24 | 14.88 / 14.76 | 220-222 | 87 |
| **1h** | $C_{22}H_{22}N_4O_3$ | 67.68 / 67.80 | 5.68 / 5.76 | 14.35 / 14.47 | 214-216 | 84 |
| **1i** | $C_{22}H_{22}N_4O_3$ | 67.68 / 67.57 | 5.68 / 5.58 | 14.35 / 14.26 | 219-221 | 88 |
| **1j** | $C_{23}H_{24}N_4O_3$ | 68.30 / 68.19 | 5.98 / 6.10 | 13.85 / 13.72 | 210-212 | 90 |
| **1k** | $C_{24}H_{26}N_4O_3$ | 68.88 / 68.75 | 6.26 / 6.11 | 13.39 / 13.52 | 194-196 | 87 |
| **1l** | $C_{25}H_{28}N_4O_3$ | 69.42 / 69.56 | 6.53 / 6.64 | 12.95 / 13.07 | 178-180 | 82 |
| **1m** | $C_{26}H_{30}N_4O_3$ | 69.93 / 70.05 | 6.77 / 6.86 | 12.55 / 12.41 | 173-175 | 84 |

More detailed information on the tautomeric transitions in solutions of benzimidazol-2-ylamides **1a-m** could undoubtedly be obtained using NMR heteronuclear correlation spectroscopy. Unfortunately, such spectra could not be taken due to the low solubility of these compounds. For the same reason, we could not study the behavior in solution of a model compound, the ethyl ester of 5-(benzimidazol-2-ylcarbamoyl)-4-hydroxy-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid (**4**). However, on the other hand, a monocrystal of the amido ester was grown from solution, which proved suitable for X-ray diffraction crystallographic structural analysis, and important information was obtained on the three-dimensional study of this class of compounds. As expected, many specific structural features were found common for primary N-R-amides of 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids [26-28]. Thus, in particular, amido ester **4** gives rise to an analogous system with strong intramolecular hydrogen bonds: 4-OH···O=C–NH and 6-C=O···HNC=O, which accounts for the existence of only the amide tautomer in the crystal, while the pyridine ring, carbamide group, and benzimidazole fragment lie in a single plane. More detailed information on the structure of amidoester **4** is given in our previous work [1]. These findings allow a high level of confidence to assert that crystalline benzimidazol-2-ylamides of 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids also exist as amide form **1a-m** exclusively.

The antithyroid properties of benzimidazol-2-ylamides **1a-m** were studied on nonpedigreed white rats (50-60 g) in parallel and in comparison with Thiamazole according to a standard procedure (see Experimental). The experimental results indicate that most of these products indeed are capable to reliably lower the concentration of thyroid hormones. In some cases, namely, amides **1a**,**b**, the activity was even higher than for the reference compound (Table 3). On the other hand, we cannot ignore that compounds with long 1N-alkyl substituents, namely, amides **1k-m**, have a completely opposite effect, leading to a significant rise in the level of triiodothyronine ($T_3$) and, to a somewhat lesser extent, thyroxin ($T_4$).

The effect of benzimidazol-2-ylamides **1a-m** on *Mycobacterium tuberculosis H37Rv* ATCC 27294 was studied radiometrically [29, 30]. Comparing the data for preliminary screening (Table 3) with the results of a

TABLE 2. $^{1}$H NMR Spectra of Benzimidazol-2-ylamides of 1-R-4-Hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic Acids **1a-m**

| Compound | Chemical shifts, δ, ppm (*J*, Hz)* | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | OH (1H, s) | CONH (1H, s) | H arom. quinoline | | | | H arom. benzimidazole | | R |
| | | | H-5 (1H, d) | H-7 (1H, t) | H-8 (1H, d) | H-6 (1H, t) | H-4,7 (2H, br. m) | H-5,6 (2H, m) | |
| **1a** | 16.10 | 13.60 | 8.13 (*J* = 8.0) | 7.70 (*J* = 7.7) | 7.40 (*J* = 8.6) | 7.24 (*J* = 7.6) | 7.47 | 7.12 (*J* = 3.0) | 10.56 (1H, s, NH) |
| **1b** | 15.95 | 13.51 | 8.22 (*J* = 8.0) | 7.79 (*J* = 7.8) | 7.55 (*J* = 8.7) | 7.32 (*J* = 7.5) | 7.49 | 7.11 (*J* = 3.0) | 3.74 (3H, s, $NCH_3$) |
| **1c** | 15.84 | 13.47 | 8.21 (*J* = 7.9 ) | 7.80 (*J* = 7.8) | 7.59 (*J* = 8.5) | 7.34 (*J* = 7.6) | 7.48 | 7.12 (*J* = 2.9) | 4.46 (2H, q, *J* = 7.1, $NCH_2$); 1.37 (3H, t, *J* = 7.1, $CH_3$) |
| **1d** | 15.87 | 13.56 | 8.20 (*J* = 7.9) | 7.81 (*J* = 7.7) | 7.58 (*J* = 8.6) | 7.33 (*J* = 7.6) | 7.47 | 7.12 (*J* = 3.0) | 5.93 (1H, m, $C\underline{H}{=}CH_2$); 5.18 (1H, d, *J* = 10.5, $NCH_2CH{=}C\underline{H}$-*cis*); 5.09 (1H, d, *J* = 17.4, $NCH_2CH{=}C\underline{H}$-*trans*); 4.98 (2H, s, $NCH_2$) |
| **1e** | 15.84 | 13.48 | 8.21 (*J* = 8.0) | 7.80 (*J* = 7.7) | 7.60 (*J* = 8.6) | 7.36 (*J* = 7.5) | 7.49 | 7.10 (*J* = 3.0) | 4.33 (2H, t, *J* = 7.3, $NCH_2$); 1.80 (2H, m, $NCH_2C\underline{H_2}$); 1.11 (3H, t, *J* = 7.0, $CH_3$) |
| **1f** | 15.72 | 13.43 | 8.22 (*J* = 7.9) | 7.79 (*J* = 7.7) | 7.59 (*J* = 8.5) | 7.37 (*J* = 7.5) | 7.50 | 7.11 (*J* = 3.0) | 4.39 (2H, t, *J* = 7.4, $NCH_2$); 1.78 (2H, quin., *J* = 7.2, $C\underline{H_2}CH_2CH_3$); 1.51 (2H, m, $CH_2\underline{CH_2}CH_3$); 1.04 (3H, t, *J* = 7.0, $CH_3$) |
| **1g** | 15.80 | 13.41 | 8.22 (*J* = 8.0) | 7.78 (*J* = 7.8) | 7.60 (*J* = 8.6) | 7.38 (*J* = 7.5) | 7.50 | 7.12 (*J* = 2.9) | 4.29 (2H, d, *J* = 6.9, $NCH_2$); 2.27 (1H, m, CH); 1.02 (6H, d, *J* = 6.4, $2CH_3$) |
| **1h** | 15.79 | 13.40 | 8.20 (*J* = 8.0) | 7.80 (*J* = 7.8) | 7.61 (*J* = 8.6) | 7.39 (*J* = 7.6) | 7.49 | 7.10 (*J* = 2.9) | 4.36 (2H, t, *J* = 7.2, $NCH_2$); 1.79 (2H, quin., *J* = 6.9, $NCH_2C\underline{H_2}$); 1.48 (4H, m, $(C\underline{H_2})_2CH_3$); 1.00 (3H, t, *J* = 6.7, $CH_3$) |
| **1i** | 15.83 | 13.45 | 8.21 (*J* = 8.0) | 7.79 (*J* = 7.7) | 7.62 (*J* = 8.5) | 7.38 (*J* = 7.6) | 7.50 | 7.12 (*J* = 3.0) | 4.38 (2H, t, *J* = 7.4, $NCH_2$); 1.81 (1H, m, CH); 1.59 (2H, q, *J* = 7.2, $NCH_2C\underline{H_2}$); 1.01 (6H, d, *J* = 6.6, $2CH_3$) |
| **1j** | 15.76 | 13.42 | 8.22 (*J* = 7.9) | 7.80 (*J* = 7.8) | 7.57 (*J* = 8.5) | 7.36 (*J* = 7.5) | 7.50 | 7.11 (*J* = 3.0) | 4.35 (2H, t, *J* = 7.2, $NCH_2$); 1.79 (2H, quin., *J* = 7.0, $NCH_2C\underline{H_2}$); 1.60-1.34 (6H, m, $(C\underline{H_2})_3CH_3$); 0.98 (3H, t, *J* = 6.7, $CH_3$) |
| **1k** | 15.70 | 13.39 | 8.20 (*J* = 8.0) | 7.80 (*J* = 7.7) | 7.55 (*J* = 8.6) | 7.37 (*J* = 7.6) | 7.49 | 7.10 (*J* = 3.0) | 4.34 (2H, t, *J* = 7.2, $NCH_2$); 1.79 (2H, quin., *J* = 7.0, $NCH_2C\underline{H_2}$); 1.57-1.32 (8H, m, $(C\underline{H_2})_4CH_3$); 0.95 (3H, t, *J* = 6.7, $CH_3$) |
| **1l** | 15.75 | 13.40 | 8.21 (*J* = 8.0) | 7.81 (*J* = 7.8) | 7.58 (*J* = 8.5) | 7.36 (*J* = 7.6) | 7.50 | 7.11 (*J* = 2.9) | 4.37 (2H, t, *J* = 7.4, $NCH_2$); 1.78 (2H, quin., *J* = 7.1, $NCH_2C\underline{H_2}$); 1.56-1.30 (10H, m, $(C\underline{H_2})_5CH_3$); 0.94 (3H, t, *J* = 6.6, $CH_3$) |
| **1m** | 15.76 | 13.39 | 8.22 (*J* = 8.1 ) | 7.80 (*J* = 7.8) | 7.57 (*J* = 8.6) | 7.39 (*J* = 7.6) | 7.50 | 7.11 (*J* = 3.0) | 4.38 (2H, t, *J* = 7.3, $NCH_2$); 1.73 (2H, quin., *J* = 7.0, $NCH_2C\underline{H_2}$); 1.55-1.28 (12H, m, $(C\underline{H_2})_6CH_3$); 0.92 (3H, t, *J* = 6.7, $CH_3$) |

* The signals of the 1-NH groups of the benzimidazole fragment appear as singlet at 11.83-12.08 ppm with intensity 1H.

TABLE 3. Biological Properties of Products **1a-m**

| Compound | Antithyroid activity, concentration of thyroid hormones in the serum of test animals | | | | Antituberculosis activity | |
|---|---|---|---|---|---|---|
| | $T_3$, nmol/l | % rel. to control* | $T_4$, nmol/l | % rel. to control* | *[2] | MIC |
| **1a** | 1.46 ± 0.13 | -25.9 | 59.7 ± 2.35 | -40.9 | 45 | – |
| **1b** | 1.50 ± 0.17 | -23.9 | 69.8 ± 3.63 | -30.9 | 100 | 1.56 |
| **1c** | 1.76 ± 0.21 | -10.7 | 75.7 ± 3.95 | -25.1 | 100 | 3.13 |
| **1d** | 1.70 ± 0.18 | -13.7 | 84.0 ± 4.11 | -16.8 | 72 | – |
| **1e** | 1.70 ± 0.22 | -13.7 | 69.9 ± 3.52 | -31.0 | 99 | 6.25 |
| **1f** | 1.97 ± 0.25 | 0 | 79.0 ± 3.74 | -218 | 79 | – |
| **1g** | 1.72 ± 0.16 | -13.5 | 64.3 ± 2.92 | -36.3 | 71 | – |
| **1h** | 1.60 ± 0.13 | -18.8 | 63.3 ± 2.57 | -37.4 | 83 | – |
| **1i** | 1.83 ± 0.20 | -7.5 | 95.4 ± 6.05 | -5.5 | 80 | – |
| **1j** | 1.77 ± 0.18 | -10.2 | 76.7 ± 4.53 | -24.1 | 99 | 3.13 |
| **1k** | 2.66 ± 0.28 | +35.5 | 120.3 ± 13.28 | +19.1 | 100 | 1.56 |
| **1l** | 2.27 ± 0.26 | +15.2 | 115.0 ± 10.67 | +13.8 | 66 | – |
| **1m** | 2.03 ± 0.19 | +3.0 | 98.0 ± 6.81 | -2.9 | 69 | – |
| Mercazolyl | 1.63 ± 0.22 | -17.3 | 74.7 ± 5.12 | -26.0 | – | – |

*The minus sign indicates a decrease and the plus sign indicates an increase in the concentration of thyroid hormones relative to the control taken as 100%.
*[2]Growth suppression, %, *Mycobacterium tuberculosis H37Rv* ATCC 27294 at concentration 6.25 μg/ml.

study of the antituberculosis properties for others diazahetarylamides of 1-R-4-hydroxy-2-oxo-1,2-di-hydro-quinoline-3-carboxylic acids, we found that the benzimidazole derivatives had significantly higher activity than compared to pyrimidine analogs [28]. On the other hand, our products were inferior to pyrazin-2-ylamides [31] both in their capacity to repress the growth of a test strain and relative to the minimal inhibiting concentration (MIC) determined only for the most active samples.

## EXPERIMENTAL

The $^1$H NMR spectra of the products synthesized were taken on a Bruker WM-360 spectrometer at 360 MHz in DMSO-$d_6$ as the solvent with TMS as the internal standard. Samples of the benzimidazol-2-ylamides of 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids **1a-m** were obtained by the reaction of ethyl esters of the corresponding quinoline-3-carboxylic acids **2a-m** with 2-aminobenzimidazole according to our previous procedure [22]. 2-Aminobenzimidazole was obtained from Fluka. The concentration of the thyroid hormones was determined on a ChemWell automatic immunoenzyme analyzer using manufactured by Xema-Medica, Ltd. in Russia standard test systems for the immunoenzyme analysis (IEA) in serum and blood plasma for total triiodothyronine ($T_3$, IEA) and thyroxin ($T_4$, IEA).

**Antithyroid activity** of benzimidazol-2-ylamides of 1-R-4-hydroxy-2-oxo-1,2-dihydro-1,2-dihydro-quinoline-3-carboxylic acids **1a-m** was studied by the standard "goiter" reaction [32] on white rats (50-60 g). The test compounds and the reference, Thiamazole, were introduced orally as a fine aqueous suspension stabilized by Twin-80 daily at the same time (8:00-9:00 AM). The dose was 10 mg/kg (the effective dose of Thiamazole). The control group of animals was maintained under analogous conditions and received distilled water

with Twin-80. The experiment lasted 10 days. The animals were sacrificed under ether narcosis on the eleventh day by instantaneous cutting of the spinal cord at the base of the brain. The blood was collected and centrifuged. The levels of triiodothyronine ($T_3$) and thyroxin ($T_4$) in the serum were determined.

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