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Three-Component Reaction of Dimedone with Aromatic Aldehydes and 5-Aminotetrazole

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Abstract—Reactions of dimedone with aromatic aldehyde and 5-aminotetrazole monohydrate proceeded with the formation of 9-aryl-6,6-dimethyl-5,6,7,9-tetrahydrotetrazolo[5,1-*b*]quinazoline-8(4*H*)-ones or 9-aryl-3,3,6,6-tetramethyl-3,4,6,7-tetrahydro-2*H*-xanthene-1,8(5*H*,9*H*)-diones depending on the nature of substituent in aromatic aldehyde. Antimicrobial, antifungal and analgesic activities of the synthesized compounds were studied.

Keywords: 9-aryl-6,6-dimethyl-5,6,7,9-tetrahydrotetrazolo[5,1-*b*]quinazolin-8(4*H*)-ones, 9-aryl-3,3,6,6-tetramethyl-9-aryl-3,4,6,7-tetraahydro-2*H*-xanthene-1,8(5*H*,9*H*)-diones, antimicrobial activity, analgesic activity

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Multicomponent reactions are a promising direction in the field of the synthesis of nitrogen-containing heterocyclic compounds, among which substances with high biological activity have been found [1]. Particular attention is drawn to quinazoline derivatives [2]. Currently, anticancer drugs (Lapatinib, Gefitinib), antiplatelet agent (Anagrelid) and α-adrenergic blocker for treatment of BPH (Alfuzosin) containing a quinazoline fragment in the structure are registered in the Russian Federation [3]. Introduction of a tetrazole ring into the molecule is of practical interest due to the possibility of further search for effective and safe preparations among this class of organic compounds. Some of the substituted tetrazoloquinazolinones show cytostatic [4], antimicrobial [5], hypoglycemic [6], and antiviral [7] activities.

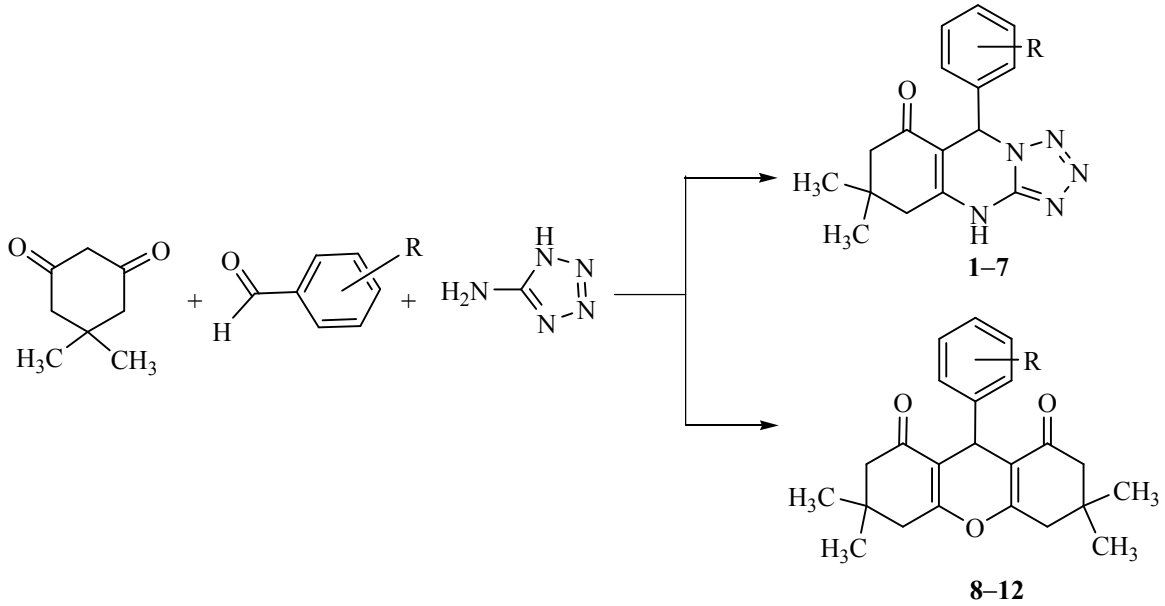
5-Aminotetrazole is a 1,3-binucleophile. It is widely used as a building block in multicomponent reactions, including the construction of condensed heterocyclic compounds of 4,7-dihydrotetrazolo[1,5-*a*]pyrimidine and tetrahydroteterazolo[5,1-*b*]quinazolin-8(4*H*)-one series in the modified Biginelli reaction [8–10].

We have previously shown that reaction of 5-aminotetrazole with aromatic aldehyde and cyclic 1,3-diketone resulted in the formation of 9-aryl-6,6-dimethyl-5,6,7,9-tetrahydroteterazolo[5,1-*b*]quinazolin-8(4*H*)-ones as the only reaction product in high yield [11]. In continuation of this research, herein we expand the range of 9-aryl-6,6-dimethyl-5,6,7,9-tetrahydrotetrazolo[5,1-*b*]quinazolin-8(4*H*)-ones and studied their biological activity. However, we found that the reaction of dimedone with a mixture of 5-aminotetrazole monohydrate and substituted aromatic aldehyde taken in an equimolar ratio without solvent and catalyst at a temperature of 160–170°C for 5–10 min afforded 9-aryl-6,6-dimethyl-5,6,7,9-tetrahydrotetrazolo[5,1-*b*]quinazolin-8(4*H*)-ones **1–7** or 9-aryl-3,3,6,6-tetramethyl-3,4,6,7-tetrahydro-2*H*-xanthen-1,8(5*H*,8*H*)-diones **8–12** (Scheme 1).

The synthesized compounds **1–7** are white or pale yellow crystalline substances soluble in DMF, DMSO, ethanol and acetic acid when heated, and insoluble in water.

The IR spectra of **1–7** contain absorption bands of stretching vibrations of the C=O group in the region of 1649–1652 cm^{-1}, and a weak absorption band in the range of 3161–3174 cm^{-1} characteristic of stretching vibrations of the N–H bond.

Scheme 1.

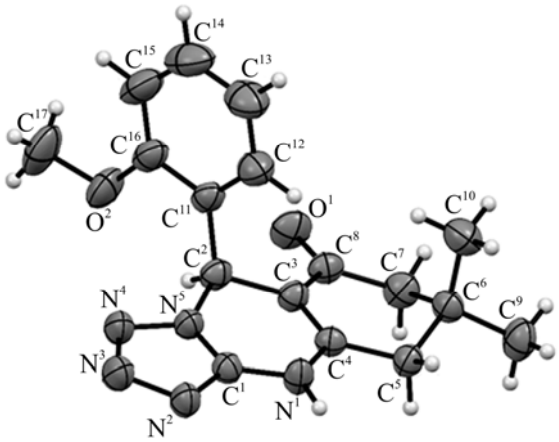


1–7

8–12

R = H (**1**), 4-CH_3 (**2**), 4-*t*-Bu (**3**), 2-CH_3O (**4**), 3,4-$(CH_3O)_2$, (**5**), 2,5-$(CH_3O)_2$ (**6**), 2-Cl (**7**), 4-CH_3O (**8**), 4-C_2H_5O (**9**), 4-Cl (**10**), 4-Br (**11**), 4-NO_2 (**12**).

In the ^{1}H NMR spectra of the obtained compounds **1–7**, in addition to signals of the aromatic protons and related groups, there are singlet signals of the protons of two methyl groups at 6-position the ring at 0.95–1.03 and 0.99–1.07 ppm, four doublets of the protons at the C^5 (2.05–2.14 and 2.21–2.25 ppm, J = 16.0–16.2 Hz) and C^7 atoms of the ring (2.49–2.59 and 2.57–2.62 ppm, J = 17.1–17.2 Hz), as well as singlet signals of the C^9H (6.54–6.89 ppm) and NH groups (11.28–11.62 ppm).



General view of the molecule of compound **4**.

Characteristic for the mass spectra of compounds **2**, **6** and **7** is the presence of strong peaks of the molecular ions with m/z 310, 356 and 330, respectively.

To confirm unambiguously the structure of tetrazolo[5,1-*b*]quinazolin-8(4*H*)-ones obtained, single crystal X-ray diffraction analysis of compound **4** was performed. Single crystals of **4** were obtained by slow crystallization from acetic acid. By XRD data, compound **4** crystallizes in the centrosymmetric space group of the triclinic syngony (see Figure). The bond lengths and the valence angles in the molecule take on the usual values for the corresponding atoms. The tetrazole ring is plane at around 0.01 Å. The cyclohexane and pyrimidine rings take the *sofa* conformation; the C^6 and C^2 atoms are out off the plane by 0.64 and 0.19 Å. In a crystal, molecules are linked into centrosymmetric dimers due to the intermolecular hydrogen bonding N^1–$H^1\cdots N^2$ (1 – x, 1 – y, –z) [N^1–H^1 0.87(2), $H^1\cdots N^2$ 2.02(2), $N^1\cdots N^2$ 2.879(3) Å, $N^1H^1N^2$ 169(2)°].

Compounds **8–12** are colorless crystalline substances, soluble in chloroform; when heated, in ethanol, insoluble in water.

In the IR spectra of compounds **8–12**, there is an absorption band of stretching vibrations of two keto groups conjugated with the double bond in the 1658–1662 cm^{-1} region.

The ^{1}H NMR spectra of compounds **8–12** contain signals of the protons of four methyl groups at positions 3 and 6 of the heterocycle (0.90–0.92 and 1.03–1.05 ppm), C^4H and C^5H (2.07–2.09 and 2.21–2.26 ppm, J = 16.0–16.4 Hz), C^2H and C^7H (2.48–2.53 and 2.54–2.59 ppm, J = 17.8–18.6 Hz), and C^9H (4.47–5.49 ppm) moieties of the ring, as well as signals of the aromatic protons.

The mass spectrum of compound **9** contains a strong peak of the molecular ion with m/z 430, as well as peaks of the corresponding fragment ions.

To confirm the structure of compounds **8–12**, a single crystal X-ray study of compound **8** was performed. Crystals of **8** were obtained by slow crystallization from acetonitrile. The resulting data confirmed the proposed structure [12].

In summary, the nature of the substituents in the aromatic aldehyde influences the reaction regioselectivity. So, in the case of the presence of electron-donating substituents, as well as the nitro group in the *para*-position, the reaction predominantly proceeds with the formation of 3,3,6,6-tetramethyl-9-aryl-3,4,5,6,7,9-hexahydro-1*H*-xanthen-1,8(2*H*)-diones **8–12**. 9-Aryl-6,6-dimethyl-5,6,7,9-tetrahydroteterazolo [5,1-*b*]quinazolin-8(4*H*)-ones **1–7** are formed as the only reaction product, when electron-donating substituents are in the *ortho* or *ortho* and *meta* positions.

1,8-Dioxooctahydroxanthene derivatives are known to possess biological activity [13]. In this regard, it was of interest to evaluate antibacterial and antifungal activity of the synthesized 9-aryl-3,3,6,6-tetramethyl-3,4,6,7-tetrahydro-2*H*-xanthen-1,8(5*H*, 8*H*)-diones.

Antimicrobial and antifungal activity of compounds **1–12** against *S. aureus* 6538P ATCC, *E. coli* 25922 ATCC and *C. albicans* ATCC 885-653 strains was studied in vitro by the method of double serial dilutions in a liquid nutrient medium. Dioxidin and fluconazole were used as comparative drugs for antimicrobial and antifungal activity, respectively. Bacterial load was 250 000 microbial units per 1 mL of solution. Evaluation of the bacteria and fungi growth was performed visually. For all the studied compounds, the minimum inhibitory concentration (MIC, μg/mL) was determined. The test compounds were found to have low antibacterial and antifungal activity with MIC equal to or greater than 1000 μg/mL.

For compound **6**, analgesic activity was determined by the acetic writhing test [14]. The obtained results showed that in control experiments in mice during the observation period, the number of writhing caused by the introduction of a 0.75% solution of acetic acid was 28.40±0.68. The use of the comparative drug metamizole sodium at a concentration of 50 mg/kg reduced this indicator by 50% (up to 14.00±0.50). With the introduction of the test compound **6** at the same concentration, the number of writhing in experimental animals during the same observation period was 4.5±0.92, therefore the number of acetic writhing decreased by 84.2%. Thus, compound 6 show analgesic activity and is superior in activity to the comparison drug (metamizole sodium).

EXPERIMENTAL

IR spectra were recorded on a Specord M-80 instrument from KBr pellets. ^{1}H NMR spectra were recorded on a Bruker AVANCE III HD 400 spectrometer from DMSO-d_6 solutions relative to internal TMS. Mass spectra were registered on a Waters ACQUITY UPLC I-Class instrument using ultra-HPLC-MS method (Acquity UPLC BEH C18 1.7 μm column, mobile phases — acetonitrile–water, flow rate 0.6 mL/min, Xevo TQD mass detector). Elemental analysis was performed on a PerkinElmer 2400 instrument. Melting points were measured on a Melting Point M-565 instrument.

X-Ray diffraction analysis of compound **4** was performed on a Xcalibur Ruby diffractometer with a CCD detector according to the standard procedure [MoK_α radiation, 295(2) K, ω-scanning in 1° increments]. The absorption is taken into account empirically using the SCALE3 ABSPACK algorithm [15]. Crystals are triclinic, space group P-1, a = 6.1721(13) Å, b = 10.980(3) Å, c = 12.634(2) Å, α = 97.732(17)°, β = 97.939(17)°, γ = 102.872(19)°, V = 814.5(3) Å^3, Z = 2. The structure was solved using the SHELXS program [16] and refined by the full-matrix least squares F^2 method in the anisotropic approximation for all non-hydrogen atoms using the SHELXL program [17] with OLEX2 graphic interface [18]. The hydrogen atom of the NH group is refined independently in an isotropic approximation. The remaining hydrogen atoms were refined using the *rider* model. Final refinement parameters: R_1 = 0.0634, wR_2 = 0.1418 [for 2269 reflections with $I > 2\sigma(I)$], R_1 = 0.1047, wR_2 = 0.1795 (for all 3739 independent reflections), S = 1.031. Crystallographic data were deposited at the Cambridge Crystallographic Data Center (CCDC 1879919).

9-Phenyl-6,6-dimethyl-5,6,7,9-tetrahydrotetrazolo[5,1-*b*]quinazolin-8(4*H*)-one (1). A mixture of 0.01 mol of dimedone, 0.01 mol of benzaldehyde and 0.01 mol of 5-aminotetrazole monohydrate was kept at a temperature of 160–170°C for 5–10 min until gas evolution completed and solidification of the reaction mixture. The residue was cooled, treated with ethyl alcohol, then filtered off and recrystallized from ethanol. Yield 1.46 g (49.5%), mp 293–295°C. IR spectrum, ν, cm^{-1}: 1649 (C=O), 3172 (NH). ^1H NMR spectrum, δ, ppm: 1.03 s and 0.99 s (6H, CH_3), 2.13 d (1H, $C^5\underline{H}_AH_B$, J = 16.2 Hz), 2.24 d (1H, $C^5H_A\underline{H}_B$, J = 16.2 Hz), 2.62 s (2H, C^7H_2), 6.6 s (1H, C^9H), 1.29 s (5H, $C_6\underline{H}_5$), 11.62 br. s (1H, NH). Found, %: C 65.22; H 5.56; N 23.87. $C_{16}H_{17}N_5O$. Calculated, %: C 65.01; H 5.76; N 23.70. M 295.34.

Compounds **2–12** were obtained similarly.

9-(4-Methylphenyl)-6,6-dimethyl-5,6,7,9-tetrahydrotetrazolo[5,1-*b*]quinazolin-8(4*H*)-one (2). Yield 1.6 g (41%), mp 271–272°C. IR spectrum, ν, cm^{-1}: 1649 (C=O), 3173 (NH). ^1H NMR spectrum, δ, ppm: 1.01 s and 1.07 s (6H, CH_3), 2.14 d (1H, $C^5\underline{H}_AH_B$, J = 16.0 Hz), 2.24 d (1H, $C^5H_A\underline{H}_B$, J = 16.0 Hz), 2.25 s (3H, $\underline{CH}_3C_6H_4$), 2.61 s (2H, C^7H_2), 6.56 s (1H, C^9H), 7.13 d and 7.17 d (4H, $CH_3C_6\underline{H}_4$, J = 8.0 Hz), 11.51 br. s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 310 (100) $[M + H]^+$. Found, %: C 65.89; H 6.01; N 22.52. $C_{17}H_{19}N_5O$. Calculated, %: C 65.95; H 16.15; N 22.63. M 309.36.

9-(4-*tert*-Butylphenyl)-6,6-dimethyl-5,6,7,9-tetrahydrotetrazolo[5,1-*b*]quinazolin-8(4*H*)-one (3). Yield 1.15 g (32.7%), mp 294–296°C. IR spectrum, ν, cm^{-1}: 1649 (C=O), 3172 (NH). ^1H NMR spectrum, δ, ppm: 1.02 s and 1.06 s (6H, CH_3), 1.23 s [9H, $C(\underline{CH}_3)_3C_6H_4$], 2.5 d (1H, $C^5\underline{H}_AH_B$, J = 16.1 Hz), 2.23 d (1H, $C^5H_A\underline{H}_B$, J = 16.1 Hz), 2.57 d (1H, $C^7\underline{H}_AH_B$, J = 17.2 Hz), 2.62 d (1H, $C^7H_A\underline{H}_B$, J = 17.2 Hz), 6.56 s (1H, C^9H), 7.19 d and 7.33 d (4H, Ar), 11.46 br. s (1H, NH). Found, %: C 68.36; H 7.01; N 19.73. $C_{20}H_{25}N_5O$. Calculated, %: C 68.15; H 7.11; N 19.92. M 351.44.

9-(2-Methoxyphenyl)-6,6-dimethyl-5,6,7,9-tetrahydrotetrazolo[5,1-*b*]quinazolin-8(4*H*)-one (4). Yield 1.42 g (44%), mp 170–172°C. IR spectrum, ν, cm^{-1}: 1649 (C=O), 3164 (NH). ^1H NMR spectrum, δ, ppm: 0.95 s and 1.05 s (6H, CH_3), 2.05 d (1H, $C^5\underline{H}_AH_B$, J = 16.2 Hz), 2.21 d (1H, $C^5H_A\underline{H}_B$, J = 16.2 Hz), 2.49 d (1H, $C^7\underline{H}_AH_B$, J = 17.1 Hz), 2.59 d (1H, $C^7H_A\underline{H}_B$, J = 17.1 Hz), 3.63 s (3H, $\underline{CH}_3OC_6H_4$), 6.67 s (1H, C^9H), 6.88 d (1H, $C^3{}_{Ar}H$, J = 6.0 Hz), 6.92 t (1H, $C^4{}_{Ar}H$, J = 6.0 Hz), 7.24 t (1H, $C^5{}_{Ar}H$, J = 6.0 Hz), 7.35 d (1H, $C^6{}_{Ar}H$, J = 6.0 Hz), 11.28 br. s (1H, NH). Found, %: C 60.54; H 5.66; N 19.92. $C_{17}H_{19}N_5O_2$. Calculated, %: C 60.79; H 5.91; N 19.71. M 325.36.

9-(3,4-Dimethoxyphenyl)-6,6-dimethyl-5,6,7,9-tetrahydrotetrazolo[5,1-*b*]quinazolin-8(4*H*)-one (5). Yield 1.12 g (31.5%), mp 244–246°C. IR spectrum, ν, cm^{-1}: 1652 (C=O), 3174 (NH). ^1H NMR spectrum, δ, ppm: 1.03 s and 1.06 s (6H, CH_3), 2.13 d (1H, $C^5\underline{H}_AH_B$, J = 16.0 Hz), 2.25 d (1H, $C^5H_A\underline{H}_B$, J = 16.0 Hz), 2.6 s (2H, C^7H_2), 3.7 s (6H, CH_3O), 6.54 s (1H, C^9H), 6.76 d (1H, $C^5{}_{Ar}H$, J = 11.6 Hz), 6.88 d (1H, $C^6{}_{Ar}H$, J = 11.6 Hz), 6.89 s (1H, $C^2{}_{Ar}H$), 11.56 br. s (1H, NH). Found, %: C 60.54; H 5.66; N 19.92. $C_{18}H_{21}N_5O_3$. Calculated, %: C 60.79; H 5.91; N 19.71. M 355.39.

9-(2,5-Dimethoxyphenyl)-6,6-dimethyl-5,6,7,9-tetrahydrotetrazolo[5,1-*b*]quinazolin-8(4*H*)-one (6). Yield 1.26 g (39%), mp 270–272°C. IR spectrum, ν, cm^{-1}: 1652 (C=O), 3161 (NH). ^1H NMR spectrum, δ, ppm: 0.96 s and 1.06 s (6H, CH_3), 2.07 d (1H, $C^5\underline{H}_AH_B$, J = 16.0 Hz), 2.23 d (1H, $C^5H_A\underline{H}_B$, J = 16.0 Hz), 2.47 s (1H, $C^7\underline{H}_AH_B$), 2.60 d (1H, $C^7H_A\underline{H}_B$, J = 16.0 Hz), 3.58 and 3.71 s (6H, CH_3O), 6.64 s (1H, C^9H), 6.82–6.96 m (3H, Ar), 11.42 br. s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 356 (100) $[M + H]^+$. Found, %: C 60.51; H 5.78; N 19.92. $C_{18}H_{21}N_5O_3$. Calculated, %: C 60.79; H 5.91; N 19.71. M 355.39

9-(2-Chlorophenyl)-6,6-dimethyl-5,6,7,9-tetrahydrotetrazolo[5,1-*b*]quinazolin-8(4*H*)-one (7). Yield 2.26 g (68%), mp 219–221°C. IR spectrum, ν, cm^{-1}: 1652 (C=O), 3174 (NH). ^1H NMR spectrum, δ, ppm: 1.02 s and 1.06 s (6H, CH_3), 2.11 d (1H, $C^5\underline{H}_AH_B$, J = 16.2 Hz), 2.21 d (1H, $C^5H_A\underline{H}_B$, J = 16.2 Hz), 2.59 s (2H, C^7H_2), 6.89 s (1H, C^9H), 7.29–7.42 m (4H, Ar), 11.55 br. s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 330 (100) $[M + H]^+$. Found, %: C 58.36; H 4.66; N 21.54. $C_{16}H_{16}ClN_5O$. Calculated, %: C 58.27; H 4.86; N 21.23. M 329.78.

9-(4-Methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7-tetrahydro-2*H*-xanthen-1,8(5*H*,9*H*)-dione (8). Yield 1.21 g (32%), mp 242–244°C. IR spectrum, ν, cm^{-1}: 1675 (C=O). ^1H NMR spectrum, δ, ppm: 0.92 s and 1.04 s (12H, CH_3), 2.08 d (2H, $C^4\underline{H}_AH_B$, $C^5\underline{H}_AH_B$, J = 16.0 Hz), 2.26 d (2H, $C^4H_A\underline{H}_B$, $C^5H_A\underline{H}_B$, J = 16.0 Hz), 2.53 s and 2.54 s (4H, C^2H_2, C^7H_2), 3.69 s (3H, CH_3O), 4.48 s (1H, C^9H), 6.77 d and 7.07 d (4H, Ar). Found, %: C 75.99; H 4.51. $C_{24}H_{28}O_4$. Calculated, %: C 75.76; H 4.42. M 380.48.

9-(4-Ethoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7-tetrahydro-2*H*-xanthen-1,8(5*H*,9*H*)-dione (9). Yield 2.56 g (64.8%), mp 204–206°C. IR spectrum, ν, cm^{-1}: 1662 (C=O). ^1H NMR spectrum, δ, ppm: 0.9 s and 1.03 s (12H, CH_3), 1.26 t (3H, $OCH_2\underline{CH_3}$, J = 7.0 Hz), 2.07 d (2H, $C^4\underline{H}_AH_B$, $C^5\underline{H}_AH_B$, J= 16.4 Hz), 2.24 d (2H, $C^4H_A\underline{H}_B$, $C^5H_A\underline{H}_B$, J= 16.4 Hz), 2.48 d (2H, $C^2\underline{H}_AH_B$, $C^7\underline{H}_AH_B$, J = 18.6 Hz), 2.54 d (2H, $C^2H_A\underline{H}_B$, $C^7H_A\underline{H}_B$, J = 18.6 Hz), 3.93 q (2H, $O\underline{CH_2}CH_3$, J = 7.0 Hz), 4.47 s (1H, C^9H), 6.73 d (2H, $C^2{}_{Ar}H$, $C^6{}_{Ar}H$, J = 8.8 Hz), 7.04 d (2H, $C^3{}_{Ar}H$, $C^5{}_{Ar}H$, J = 8.8 Hz). Found, %: C 76.31; H 7.72. $C_{25}H_{30}O_4$. Calculated, %: C 76.05; H 7.61. M 394.50.

9-(4-Chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7-tetrahydro-2*H*-xanthen-1,8(5*H*,9*H*)-dione (10). Yield 1.7 g (45%), mp 229–231°C. IR spectrum, ν, cm^{-1}: 1658 (C=O). ^1H NMR spectrum, δ, ppm: 0.9 s and 1.03 s (12H, CH_3), 2.08 d (2H, $C^4\underline{H}_AH_B$, $C^5\underline{H}_AH_B$, J = 16.4 Hz), 2.25 d (2H, $C^4H_A\underline{H}_B$, $C^5H_A\underline{H}_B$, J= 16.4 Hz), 2.52 s and 2.54 s (4H, C^2H_2, C^7H_2), 4.51 s (1H, C^9H), 7.17 d and 7.25 d (4H, Ar). Found, %: C 71.96; H 6.27. $C_{23}H_{25}ClO_3$. Calculated, %: C 71.71; H 6.49. M 384.90.

9-(4-Bromophenyl)-3,3,6,6-tetramethyl-3,4,6,7-tetrahydro-2*H*-xanthen-1,8(5*H*,9*H*)-dione (11). Yield 2.11 g (49.2%), mp 233–235°C. IR spectrum, ν, cm^{-1}: 1656 (C=O). ^1H NMR spectrum, δ, ppm: 0.9 s and 1.05 s (12H, CH_3), 2.09 s and 2.21 s (4H, C^4H_2, C^5H_2), 2.51 s and 2.53 s (4H, C^2H_2, C^7H_2), 5.49 s (1H, C^9H), 7.15–7.27 m (4H, Ar). Mass spectrum, m/z (I_{rel}, %): 430 (100) $[M + H]^+$. Found, %: C 64.51; H 5.66. $C_{23}H_{25}BrO_3$. Calculated, %: C 64.23; H 5.82. M 429.35.

9-(4-Nitrophenyl)-3,3,6,6-tetramethyl-3,4,6,7-tetrahydro-2*H*-xanthen-1,8(5*H*,9*H*)-dione (12). Yield 1.91 g (48.35%), mp 221–223°C. IR spectrum, ν, cm^{-1}: 1662 (C=O). ^1H NMR spectrum, δ, ppm: 0.9 s and 1.04 s (12H, CH_3), 2.09 d (2H, $C^4\underline{H}_AH_B$, $C^5\underline{H}_AH_B$, J= 16.0 Hz), 2.27 d (2H, $C^4H_A\underline{H}_B$, $C^5H_A\underline{H}_B$, J= 16.0 Hz), 2.53 d (2H, $C^2\underline{H}_AH_B$, $C^7\underline{H}_AH_B$, J = 17.8 Hz), 2.59 d (2H, $C^2H_A\underline{H}_B$, $C^7H_A\underline{H}_B$, J = 17.8 Hz), 4.64 s (1H, C^9H), 7.45 d (2H, $C^2{}_{Ar}H$, $C^6{}_{Ar}H$, J= 8.8 Hz), 8.08 d (2H, $C^3{}_{Ar}H$, $C^5{}_{Ar}H$, J = 8.8 Hz). Found, %: C 69.85; H 6.17; N 3.67. $C_{23}H_{25}NO_5$. Calculated, %: C 69.79; H 6.32; N 3.54. M 395.45.

This work was performed in compliance with all applicable international, national and institutional guidelines for the care and use of animals.

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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