ОРГАНИЧЕСКАЯ ХИМИЯ

UDC: 547.735.854.218.07:542.924

F. A. ZULPANOV, A. R. KHURRAMOV, KH. M. BOBAKULOV, B. ZH. ELMURADOV

EFFICIENT SYNTHESIS OF HOMOLOGOUS OF 3-ALKYL 2-METHYLQUINAZOLIN-4-ONES

Akad. S. Yu. Yunusov Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan. 77, Mirzo Ulugbek str., 100170, Tashkent, Uzbekistan. E-mail: zulpanovf@gmail.com tel: +998933330072

Admission date 16.02.2024

Abstract. *Background.* As a result of studying the synthesis and biological activity of condensed heterocyclic compounds, new drugs have been developed, including derivatives of 3-alkyl-2-methylquinazolin-4-one, and their bioactive derivatives have been identified. The development of new drugs based on them is relevant.

Purpose. Development of a method for the synthesis of initial 2-methylquinazolin-4-ones by heterocyclization reaction and, on their basis, the synthesis of 3(H)-substituted 2-methylquinazolin-4-ones in the presence of alkylating agents. Determination of the structures of the obtained substances using IR, 1H and 13C NMR methods.

Methodology. 3-alkyl 2-methylquinazolin-4-ones were synthesized on the basis of 2-methylquinazolin-4-one (2,3-dimethylquinazolin-4-one and other compounds, they were studied by physical methods: IR, 1H and 13C NMR, factors influencing on the course of reactions.

Originality. An improved method for the synthesis of 2-methylquinazolin-4-one has been developed using a heterocyclization reaction. New representatives of alkyl compounds have been synthesized.

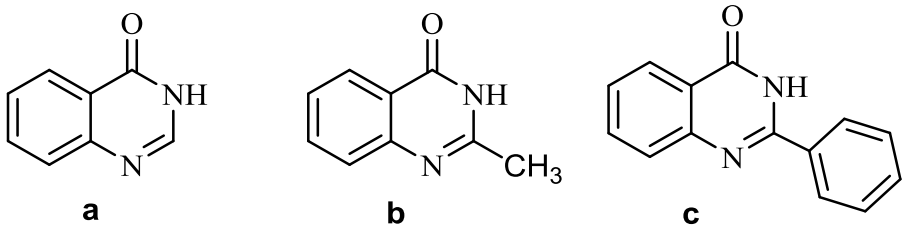
Findings. A method for the synthesis of 2-methylquinazolin-4-one with high yields has been developed, and new derivatives of 3-alkyl-2-methylquinazolin-4-ones based on this substance have been synthesized. Their structure has been studied by physical methods, and their compliance with the proposed structure has been proven.

Key words: o-aminobenzoic acid, thioacetamide, cyclization, alkyl halides, alkylation, 2-methylquinazolin 4-one, 3-alkyl-2-methylquinazolin-4-one, IR, 1H and 13C NMR.

Highlights:

- heterocyclization in the presence of o-aminobenzoic acid, thioacetamide;
- synthesis of 3-alkyl-2-methylquinazolin-4-ones in the presence of 2-methylquinazolin-4-one alkyl halides;
- the structure was studied using IR, 1H and 13C NMR spectroscopy.

Introduction. In recent years, various periparations based on many representatives of derivatives formed on the basis of heterocyclic compounds containing quinazoline have been introduced into agricultural and medical practice. Compounds based on quinazoline are widely used against viruses, microbes, fungi, colds and cancer [1], and as stimulants for plants [2]. In recent years, the incidence of socially significant diseases: cardiovascular diseases [3], diabetes [4], cancer [5] and viral diseases [6] has been increasing. An example of this is that quinazoline is included in such drugs as imatinib [7], erlotinib [8], afatinib [9], gefitinib [8,10,11], which are used against tuberculosis and cancer. In lung cancer, it increased overall survival by 19% and improved progression-free survival (PFS) by 29% compared to chemotherapy [12]. These data were approved by the United States Food and Drug Administration (FDA) [13]. Anticancer drugs prepared from compounds of the quinazoline family have shown a very low level of toxicity [14,15]:



The presence of reactive centers in the molecule of the compounds containing the quinazolone ring: N-1, N-3 nitrogen atoms, C-4 carbonyl group and C-5 and C-8 positions of the condensed benzene ring allows to conduct nucleophilic and electrophilic exchange reactions with them [16-19]. In this regard, especially the N-3 state electrophilic substitution reactions, i.e. synthesis of new types of derivatives with various halogen compounds of alkyl halides, and with the change of their functional group, it is possible to find new types of fundamental systematic laws, and among them, bioactive compounds.

Method and materials. Solvents: chloroform, hexane, cyclohexane, benzene, ethyl alcohol, methyl alcohol were dried and purified according to literature data [14]. NMR spectra were recorded on a JNM-ECZ400R spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) in DMSO-d_6+CCl_4, $CDCl_3$ and CD_3OD. TMS (δ 0.00 ppm) was used as an internal standard for ^{1}H NMR shifts, and solvent signals (DMSO-d_6 - 39.52 ppm, $CDCl_3$ - 77.16 ppm and CD_3OD - 49.00 ppm vs. TMS) were used as a reference for ^{13}C NMR shifts. IR spectra were recorded on an FT-IR/NIR Spectrum 3 IR-Fourier spectrometer (Perkin Elmer) with using attenuated total reflection. Synthesized compounds were checked by thin layer chromatography (TLC) on «Sorbfil» (Russia) and «Whatman® UV-254» (Germany) plates, and as eluents benzene: acetone - 3:1, chloroform:methanol was used in the ratio of 8:1. The melting points of the synthesized compounds was determined using «Boetius» (Germany) and «MEL-TEMP» (USA) instruments.

2-Methylquinazolin-4-one (1). 1.37 g (0.01 mole) of o-aminobenzoic acid and 1.52 g (0.02 mole) of thioacetamide were added to a 100 mL round bottom flask and heated for 2-3 hours in an oil bath connected with a reflux condenser at 140-145°C, first it boils and then a solid was formed. The obtained solid was thoroughly rubbed in a mortar, 40 ml of 5% aqueous NaOH solution was added, completely dissolved and brought to neutral medium (pH-7 by a weak solution of HCl. The precipitate was filtered and washed with distilled water. The substance was recrystallized from ethyl alcohol (C_2H_5OH) and as a yield 1.56 g (98%) of substance (**1**) with melting point (m.p.) 238-140°C, Rf=0.73 (solvent system: chloroform:methanol - 10:1) was obtained. IR spectrum (ν, cm^{-1}): 1450 cm^{-1} (C-N), 2979 cm^{-1} (C-H), 2990 cm^{-1} (CH_2), 1669 cm^{-1} (C=O), 1609 cm^{-1} (C=N). ^{1}H NMR (400 MHz, DMSO-d6+CCl_4, δ, ppm, *J*/Hz): 8.06 (1H, ddd, *J*=7.9, 1.6, 0.6, H-5), 7.65 (1H, m, H-7), 7.49 (1H, m, H-8), 7.34 (1H, m, H-6), 5.72 (1H, br. s, NH), 2.36 (3H, s, H-9). ^{13}C NMR (100 MHz, DMSO-d6+CCl_4, δ, ppm): 154.24 (C-2), 162.24 (C-4), 120.74 (C-4a), 126.24 (C-5), 124.80 (C-6), 133.10 (C-7), 125.52 (C-8), 149.12 (C-8a), 21.45 (C-9).

2,3-Dimethylquinazolin-4-one (2). Method A: 3.2 g (0.02 mole) of 2-methylquinazolin-4-one, 30 ml of ethyl alcohol (C_2H_5OH) and 1.232 g (0.022 mole) of KOH were plased in a 100 ml round-bottomed flask and boiled and slightly mixed. The reaction mixture was cooled and 3.74 ml (0.06 mole) (8.52 g, d=2.28 g/ml) methyl iodide (CH_3I) was added and heated at 75-80°C for 8 hours. The resulting reaction mixture was cooled and mixed by adding 30 ml of an aqueous solution of 5% NaOH, and then 70 ml of chloroform was poured over it and was stirred for 5-10 minutes, and the chloroform layer was separated using a separatory funnel. Chloroform was removed, and the resulting substance was filtered by adding activated carbon in ethyl alcohol (C_2H_5OH) and the liquid part was evaporated and recrystallized. As a yield, 0.94 g (27%) of product (**2**) was obtained with m.p. 103-105°C, Rf=0.57 (benzene:acetone – 3:1).

Method B: 1.6 g (0.01 mole) 2-methylquinazoline 4-one, 20 ml dimethylformamide (DMF), 0.672 g (0.012 mole) KOH, 1.87 ml (4.27 g d=2.28 g/ml, 0.03 mole) methyl iodide (CH_3I) was added and stirred at room temperature for 15 min and heated at 40-45°C for 4 hours with a magnetic stirrer and reflux condenser connected. The resulting mixture was poured onto ice and the precipitate was filtered off, then washed in an aqueous solution of 5% NaOH. The material was recrystallized from cyclohexane. As a yield, 1.62 g (93%) of substance (**2**) was obtained. IR spectrum (KBr, ν, cm^{-1}):2985 (CH), 2925 (CH_2), 1653 (C=O), 1598 (C=N), 1478 (C-N). ^{1}H NMR (400 MHz, CD_3OD, δ, ppm. J/Hz): 8.00 (1H, ddd, J=8.1, 1.6, 0.6, H-5), 7.67 (1H, ddd, J=8.5, 7.1, 1.5, H-7), 7.44 (1H, ddd, J=8.5, 1.2, 0.6, H-8), 7.37 (1H, ddd, J=8.2, 7.1, 1.2, H-6), 3.50 (3H, s, H-1`), 2.52 (3H, s, H-9).$^{13}$C NMR (100 MHz, $CD_3OD$, δ, ppm): 157.51 (C-2), 163.60 (C-4), 120.86 (C-4a), 127.64 (C-5), 126.87 (C-6), 135.57 (C-7), 127.40 (C-8), 148.01 (C-8a), 23.13 (C-9), 31.50 (C-1`).

2-Methyl-3-ethylquinazolin-4-one (3). 1.6 g (0.01 mole) of 2-methylquinazolin-4-one, 30 ml of ethyl alcohol (C_2H_5OH) and 1.232 g (0.022 mole) of KOH were placed in a 100 ml round-bottom flask and was slightly mixed. After cooling the reaction mixture, 1.94 ml (2.85 g, d=1.47 g/ml) (0.015 mole) ethyl bromide (C_2H_5Br) was added and heated at 75-80°C for 7 hours. The resulting reaction mixture was cooled and mixed with 30 ml of 5% NaOH aqueous solution, and 60 ml of chloroform was added and extracted. After chloroform extraction, the substance was recrystallized from ethyl alcohol. As a yield, 1.56 g (83%) of substance (**3**) was obtained with m.p. 95-97°C, R_f=0.53 (benzene:acetone – 3:1). IR spectrum (KBr, ν, cm^{-1}): 2993 (C-H), 2927 (CH_2), 1656 (C=O), 1642 (C=N), 1469 (C-N). ^{1}H NMR (400 MHz, CD_3OD, δ, ppm, J/Hz): 8.09 (1H, ddd, J=8.1, 1.5, 0.6, H-5), 7.69 (1H, ddd, J=8.4, 7.1, 1.5, H-7), 7.51 (1H, ddd, J=8.4, 1.1, 0.6, H-8), 7.41 (1H, ddd, J=8.1, 7.1, 1.1, H-6), 4.13 (2H, q, J=7.1, H-1`), 2.61 (3H, s, H-9), 1.30 (2H, t, J=7.1, H-2`). ^{13}C NMR (100 MHz, CD_3OD, δ, ppm): 156.87 (C-2), 163.32 (C-4), 121.30 (C-4a), 127.75 (C-5), 126.99 (C-6), 135.68 (C-7), 127.41 (C-8), 148.16 (C-8a), 22.61(C-9), 40.91 (C-1`), 13.77 (C-2`).

2-Methyl-3-iso-amylquinazolin-4-one (4). 1.6 g (0.01 mole) of 2-methylquinazolin-4-one, 30 ml of ethyl alcohol (C_2H_5OH) and 0.672 g (0.012 mole) of KOH were placed in a 100 ml round-bottom flask and slightly mixed. After cooling the reaction mixture, 1.4 ml (1.6 g, d=0.87 g/ml) (0.015 mole) of iso-amyl chloride ($C_5H_{11}Cl$) was added and heated at 75-80°C for 9 hours. The resulting reaction mixture was cooled and mixed with 30 ml of 5% NaOH aqueous solution, and 70 ml of chloroform was poured into it for extraction. As a yield, 2.2 g (83%) of substance (**4**) was obtained with m.p. 65-67°C, R_f=0.68 (benzene:acetone – 3:1). IR spectrum (KBr, ν, cm^{-1}): 2957 (CH), 2925 (CH_2), 1669 (C=O), 1572 (C=N), 1469 (C-N). ^{1}H NMR (400 MHz, CD_3OD+CCl_4, δ, ppm, J/Hz): 8.09 (1H, ddd, J=8.0, 1.6, 0.6, H-5), 7.68 (1H, ddd, J=8.5, 7.1, 1.6, H-7), 7.50 (1H, ddd, J=8.2, 1.2, 0.6, H-8), 7.40 (1H, ddd, J=8.1, 7.1, 1.2, H-6), 4.05 (2H, m, H-1`), 2.59 (3H, s, H-9), 1.70 (1H, m, H-3`), 1.55 (2H, m, H-2`), 0.98 (6H, d, J=6.6, H-4`,5`). $^{13}$C NMR (100 MHz, $CD_3OD$+$CCl_4$, δ, m.u.): 156.87 (C-2), 162.88 (C-4), 121.17 (C-4a), 127.49 (C-5), 126.92 (C-6), 135.31 (C-7), 127.46 (C-8), 147.85 (C-8a), 22.80 (C-9), 44.12 (C-1`), 38.15 (C-2`), 27.44 (C-3`), 22.99 (C-4`, 5`).

2-Methyl-3-amylquinazolin-4-one (5). 1.6 g (0.01 mole) of 2-methylquinazolin-4-one, 25 ml of ethyl alcohol (C_2H_5OH) and 0.72 g (0.013 mole) of KOH were placed in a 100 ml round-bottom flask and slightly heated. After cooling the reaction mixture, was added 2.42 ml (2.132 g, d=0.88 g/ml) (0.02 mole) of amyl chloride ($C_5H_{11}Cl$) and was heated at 75-80°C for 9 hours. The resulting reaction mixture was cooled, mixed with 40 ml of 5% NaOH aqueous solution and was extracted with 50 ml of chloroform, the chloroform layer was separated, the substance formed by driving off chloroform was recrystallized from ethyl alcohol (C_2H_5OH). As a yield, 2.23 g (84%) of substance (**5**) is obtained, melting point 60-62°C, R_f=0.70 (benzene:acetone – 4:1). IR spectrum (KBr, ν, cm^{-1}): 2955 (CH), 2928 (CH_2), 1671 (C=O), 1591 (C=N), 1465 (C-N). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, *J*/Hz): 8.25 (1H, ddd, *J*=8.0, 1.6, 0.6, H-5), 7.71 (1H, ddd, *J*=8.1, 7.2, 1.6, H-7), 7.60 (1H, ddd, *J*=8.1, 1.2, 0.6, H-8), 7.43 (1H, ddd, *J*=8.1, 7.0, 1.2, H-6), 4.07 (2H, m, H-1`), 2.65 (3H, s, H-9), 1.74 (2H, m, H-2`), 1.41 (2H, m, H-3`), 1.40 (2H, m, H-4`), 0.93 (3H, t, *J*=7.2, H-5`). $^{13}$C NMR (100 MHz, $CDCl_3$, δ, ppm): 154.22 (C-2), 162.09 (C-4), 120.63 (C-4a), 126.84 (C-5), 126.42 (C-6), 134.22 (C-7), 126.64 (C-8), 147.35 (C-8a), 23.24 (C-9), 44.75 (C-1`), 28.43 (C-2`), 29.19 (C-3`), 22.43 (C-4`), 14.05 (C-5`).

2-Methyl-3-hexylquinazolin-4-one (6). 1.6 g (0.01 mole) of 2-methylquinazolin-4-one, 30 ml of ethyl alcohol (C_2H_5OH) and 0.672 g (0.012 mole) of KOH were placed in a 100 ml round-bottom flask and was slightly mixed. After cooling the reaction mixture, was added 2.21 ml (1.92 g, d=0.87 g/ml) (0.016 mole) of hexyl chloride ($C_6H_{13}Cl$) and was heated at 75-80°C for 9 hours. The resulting reaction mixture was cooled, mixed with 40 ml of an aqueous solution of 5% NaOH, and was extracted with 65 ml of chloroform. As a yield, 2.23 g (80%) of substance (**6**) was obtained with m.p. 59-60°C, R_f=0.65 (benzene:acetone – 4:1). IR spectrum (KBr, ν, cm^{-1}): 2952 (CH), 2925 (CH_2), 1671 (C=O), 1590 (C=N), 1471 (C-N). ^{1}H NMR (400 MHz, DMSO-d6+CCl_4, δ, ppm, *J*/Hz): 8.08 (1H, ddd, *J*=8.0, 1.6, 0.6, H-5), 7.67 (1H, ddd, *J*=8.2, 7.0, 1.6, H-7), 7.49 (1H ddd, 8.2, 1.3, 0.6, H-8), 7.38 (1H, ddd, *J*=8.2, 7.1, 1.2, H-6), 4.00 (2H, m, H-1`), 2.59 (3H, s, H-9), 1.66 (2H, m, H-2`), 1.40 (2H, m, H-3`), 1.36 (2H, m, H-5`), 1.35 (2H, m, H-4`), 0.91 (3H, t, *J*=7.1, H-6`). ^{13}C NMR (100 MHz, DMSO-d6+CCl_4, δ, ppm): 153.59 (C-2), 160.57 (C-4), 120.06 (C-4a), 126.18 (C-5), 125.32 (C-6), 133.17 (C-7), 126.00 (C-8), 146.91 (C-8a), 22.37 (C-9), 43.66 (C-1`), 27.98 (C-2`), 26.05 (C-3`), 30.83 (C-4`), 21.96 (C-5`), 13.63 (C-6`).

2-Methyl-3-heptylquinazolin-4-one (7). 1.6 g (0.01 mole) of 2-methylquinazolin-4-one, 30 ml of ethyl alcohol (C_2H_5OH) and 0.728 g (0.013 mole) of KOH were placed in a 100 ml round-bottom flask and was slightly mixed. After cooling the reaction mixture, 2.78 ml (2.423 g, d=0.87 g/ml) (0.018 mole) of heptyl chloride ($C_7H_{15}Cl$) was added and boiled at 75-80°C for 9 hours. The resulting reaction mixture was cooled, mixed with 30 ml of an aqueous solution of 5% NaOH and was extracted with 60 ml of chloroform. As a yield, 2.5 g (85%) of substance (**7**) was obtained with m.p. 55-57°C, R_f 0.65 (benzene:acetone – 3:1).

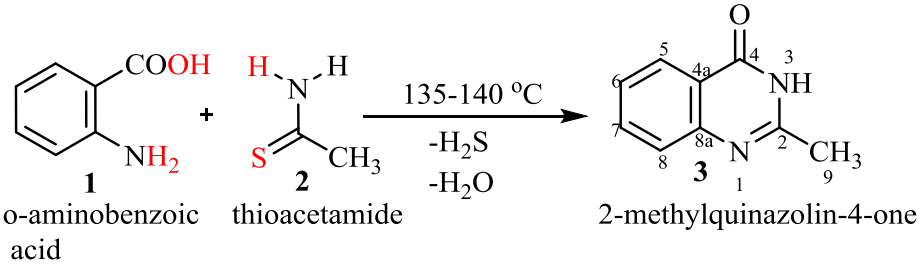
IR spectrum (KBr, ν, cm^{-1}): 2951 (CH), 2915 (CH_2), 1677 (C=O), 1591 (C=N), 1464 (C-N). ^{1}H NMR (400 MHz, DMSO-d6+CCl_4, δ, ppm, *J*/Hz): 8.04 (1H, m, H-5), 7.63 (1H, m, H-7), 7.45 (1H, m, H-8), 7.34 (1H, m, H-6), 3.96 (2H, m, H-1`), 2.55 (3H, s, H-9), 1.62 (2H, m, H-2`), 1.35 (2H, m, H-4`), 1.28 (2H, m, H-3`), 1.28 (2H, m, H-6`), 1.26 (2H, m, H-5`), 0.86 (3H, t, *J*=7.0, H-7`). $^{13}$C NMR (100 MHz, DMSO-d6+$CCl_4$, δ, ppm): 153.57 (C-2), 160.61 (C-4), 120.09 (C-4a), 126.05 (C-5), 125.37 (C-6), 133.23 (C-7), 126.22 (C-8), 146.94 (C-8a), 22.44 (C-9), 43.70 (C-1`), 28.08 (C-2`), 26.40 (C-3`), 28.39 (C-4`), 31.19 (C-5`), 22.05 (C-6`), 14.43 (C-7`).

2-Methyl-3-octylquinazolin-4-one (8). 1.6 g (0.01 mole) of 2-methylquinazolin-4-one, 30 ml of ethyl alcohol (C_2H_5OH) and 0.784 g (0.014 mole) of KOH were placed in a one-mouth 100 ml round-bottom flask and was slightly heated. After cooling the reaction mixture, was added 1.74 ml (2.38 g, d=0.87 g/ml) (0.016 mole) octyl chloride ($C_8H_{17}Cl$) and was heated at 75-80°C for 9 hours. The resulting reaction mixture was cooled and mixed with 50 ml of an aqueous solution of 5% NaOH on top and was extracted with 70 ml of chloroform, the chloroform layer was isolated, the chloroform expelled substance was recrystallized from ethanol and 2.65 g (86%) substance (**8**) was obtained with m.p. 55-57°C, R_f=0.63 (benzene:acetone-4:1). IR spectrum (KBr, ν, cm^{-1}): 2952 (CH), 2914 (CH_2), 1680 (C=O), 1590 (C=N), 1461 (C-N). ^{1}H NMR (400 MHz, CD_3OD, δ, ppm, *J*/Hz): 8.10 (1H, ddd, *J*=8.0, 1.5, 0.6, H-5), 7.71 (1H, ddd, *J*=8.3, 7.1, 1.5, H-7), 7.52 (1H, ddd, *J*=8.2, 1.2, 0.6, H-8), 7.42 (1H, ddd, *J*=8.1, 7.1, 1.1, H-6), 4.04 (2H, m, H-1`), 2.60 (3H, s, H-9), 1.66 (2H, m, H-2`), 1.35 (2H, m, H-3`), 1.28 (2H, m, H-7`), 1.26 (2H, m, H-6`), 1.25 (2H, m, H-5`), 1.23 (2H, m, H-4`), 0.83 (3H, t, *J*=7.0, H-8`). ^{13}C NMR (100 MHz, CD_3OD, δ, ppm): 156.97 (C-2), 163.49 (C-4), 121.30 (C-4a), 127.77 (C-5), 127.02 (C-6), 135.69 (C-7), 127.48 (C-8), 148.18 (C-8a), 22.76 (C-9), 45.78 (C-1`), 28.01 (C-2`), 27.95 (C-3`), 30.31 (C-4`), 30.27 (C-5`), 32.92 (C-6`), 23.67 (C-7`), 14.43 (C-8`).

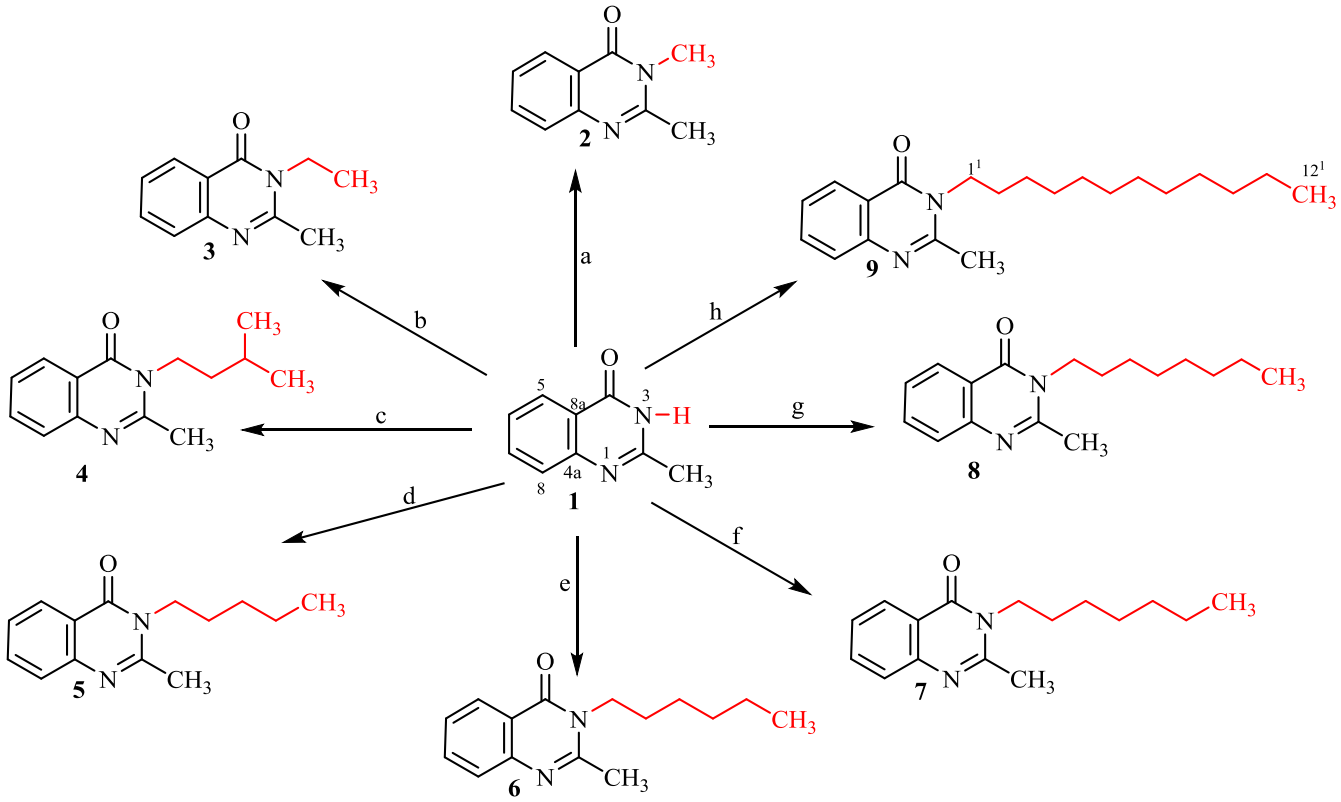
2-Methyl-3-dodecylquinazolin-4-one (9). 1.6 g (0.01 mole) of 2-methylquinazolin-4-one, 30 ml of ethyl alcohol (C_2H_5OH) and 0.896 g (0.016 mole) of KOH were placed in a 100 ml round-bottom flask and was slightly mixed. The reaction mixture was cooled and 3.36 ml (3.49 g, d=1.04 g/ml) (0.014 mole) of dodecyl chloride ($C_{12}H_{25}Cl$) was added and heated at 75-80°C for 9 hours. The resulting reaction mixture was cooled, mixed with 30 ml of 5% NaOH aqueous solution and was extracted with 70 ml of chloroform, the chloroform layer was separated, and the resulting substance was recrystallized from ethyl alcohol. As a yield, 3.59 g (88%) of substance (9) was obtained with m.p. 50-52°C, Rf=0.60 (benzene:acetone – 4:1). IR spectrum (KBr, ν, cm^{-1}): 3061 (CH), 2957 (CH_2), 1661 (C=O), 1558 (C=N), 1458 (C-N). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm., *J*/Hz): 8.22 (1H, ddd, *J*=8.1, 1.6, 0.6, H-5), 7.69 (1H, ddd, *J*=8.4, 7.1, 1.6, H-7), 7.58 (1H, ddd, *J*=8.3, 1.2, 0.6, H-8), 7.41 (1H, ddd, *J*=8.2, 7.1, 1.2, H-6), 4.05 (2H, m, H-1`), 2.63 (3H, s, H-9), 1.71 (2H, m, H-2`), 1.39 (2H, m, H-3`), 1.33 (2H, m, H-5`), 1.30 (2H, m, H-6`), 1.25 (6H, m, H-8`, 9`, 11`), 1.24 (4H, m, H-4`, 7`), 1.23 (2H, m, H-10`), 0.86 (3H, t, *J*=7.0, H-12`). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 154.28 (C-2), 162.14 (C-4), 120.67 (C-4a), 126.88 (C-5), 126.48 (C-6), 134.27 (C-7), 126.66 (C-8), 147.37 (C-8a), 23.28 (C-9), 44.84 (C-1`), 28.79 (C-2`), 27.15 (C-3`), 29.67 (C-4`), 29.38 (C-5`), 29.46 (C-6`), 29.73 (C-7`), 29.73 (C-8`), 29.63 (C-9`), 32.03 (C-10`), 22.81 (C-11`), 14.25 (C-12`).

Results and discussion. Bicyclic 2-methylquinazolin-4-ones are of great practical and theoretical interest. Among the derivatives of quinazolin-4-ones, biologically active compounds have been identified, which are used in medicine and agriculture against various harmful microorganisms. Therefore, it is very important to create efficient synthesis methods of new potentially biologically active derivatives of this class of compounds. For this purpose, in our research, we have identified convenient and effective methods of heterocyclization reaction involving o-aminobenzoic acid and thioacetamide. For this purpose, we considered it appropriate to synthesize new alkyl derivatives as a yield of carrying out electrophilic exchange reactions in the 3-position of 2-methylquinazolin-4-one, to determine the regularities in the homologous series of introduced alkyl compounds.

Initially, when 2-methylquinazolin-4-one was heated in the presence of o-aminobenzoic acid and thioacetamide, H_2S gas and water are separated. As a result of the reaction, we managed to obtain substance **3** in a quantitative yield (98%).



Various new types of alkyl compounds were synthesized by interacting 2-methylquinazolin-4-one with alkyl halides in the 3rd state. This work was carried out in an oil bath at 70-80°C with the participation of various homologues of alkyl halides (Scheme 1).



a) methyl iodide; b) ethyl bromide; c) iso-amyl chloride; d) amyl chloride;
e) hexyl chloride; f) heptyl chloride; g) octyl chloride; h) dodecyl chloride.

Scheme 1. Reactions of obtaining alkyl products of 2-methylquinazolin-4-one

The deficit of electrons in the condensed ring in the compounds stored by the bicyclic pyrimidine ring and the carbonyl group in the 4th case increases the mobility of the hydrogen atom in the 3rd case due to the high electronegative of the oxygen atom in the carbonyl group, and therefore the easy formation of HX (X-halogen) under the action of alkyl halides can be seen. Moreover, their susceptibility to (3) nucleophilic substitution reactions is evidence that they are one of the important synthons for modern organic synthesis. Their structure was investigated using physical research methods.

The chemical structures of the alkyl derivatives of 2-methylquinazolin-4-one were determined based on the analysis of ^{1}H and ^{13}C NMR spectra. In the ^{1}H NMR spectra of the synthesized alkyl derivatives (4-9), along with the signals of 2-methylquinazolin-4-one, resonance signals of the methylene group protons connected with the nitrogen atom were observed in the form of multiplet signals in the range of δ_H 3.96 – 4.07 ppm. The remaining methylene groups were resonated in the range of δ_H 1.23 – 2.65 ppm. Proton signals of terminal methyl groups were observed in the range δ_H 0.83 – 0.98 ppm. Similarly, in a high-field of ^{13}C NMR spectra of alkyl derivatives of 2-methylquinazolin-4-one, are additionally observed corresponding carbon signals of alkyl radicals. ^{1}H and ^{13}C NMR spectra of 3-dodecyl-2-methylquinazoline 4-one (9) are given as an example in Fig. 1 and 2.

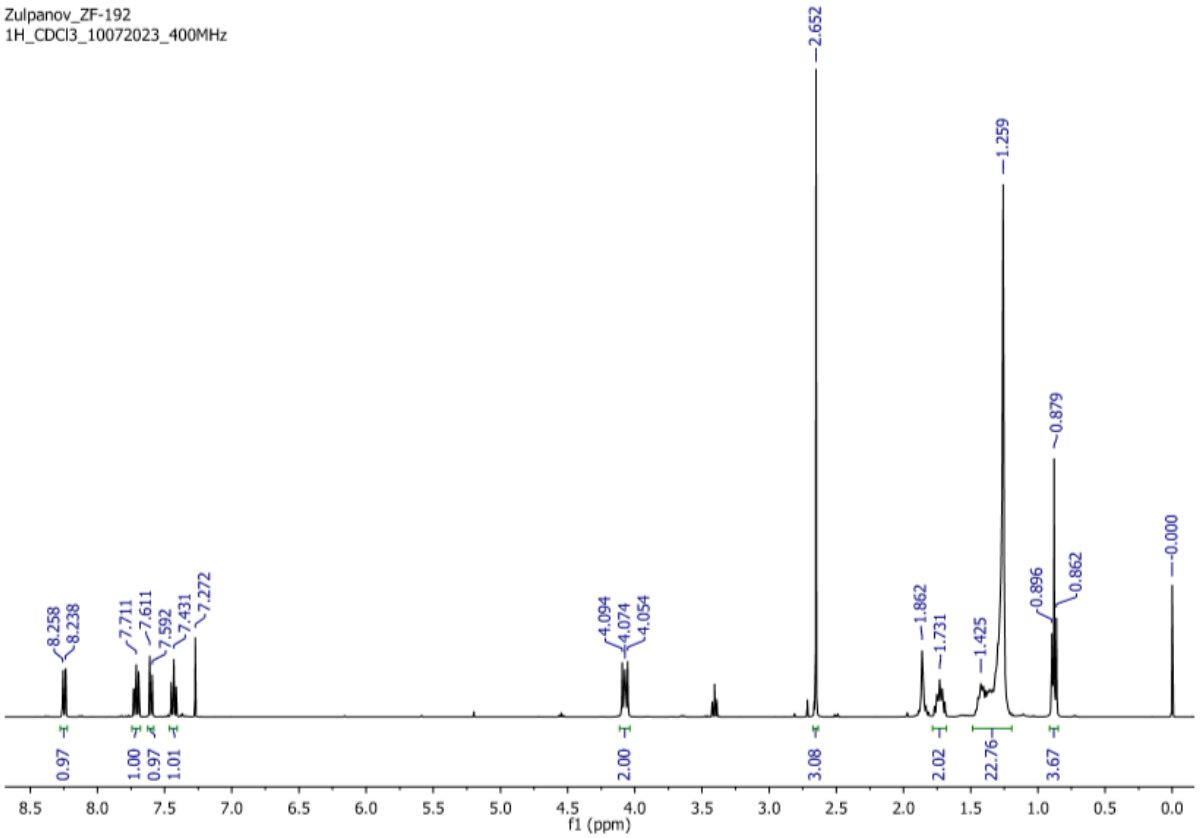


*Fig. 1. ^{1}H NMR spectrum of compound **9** in $CDCl_3$*

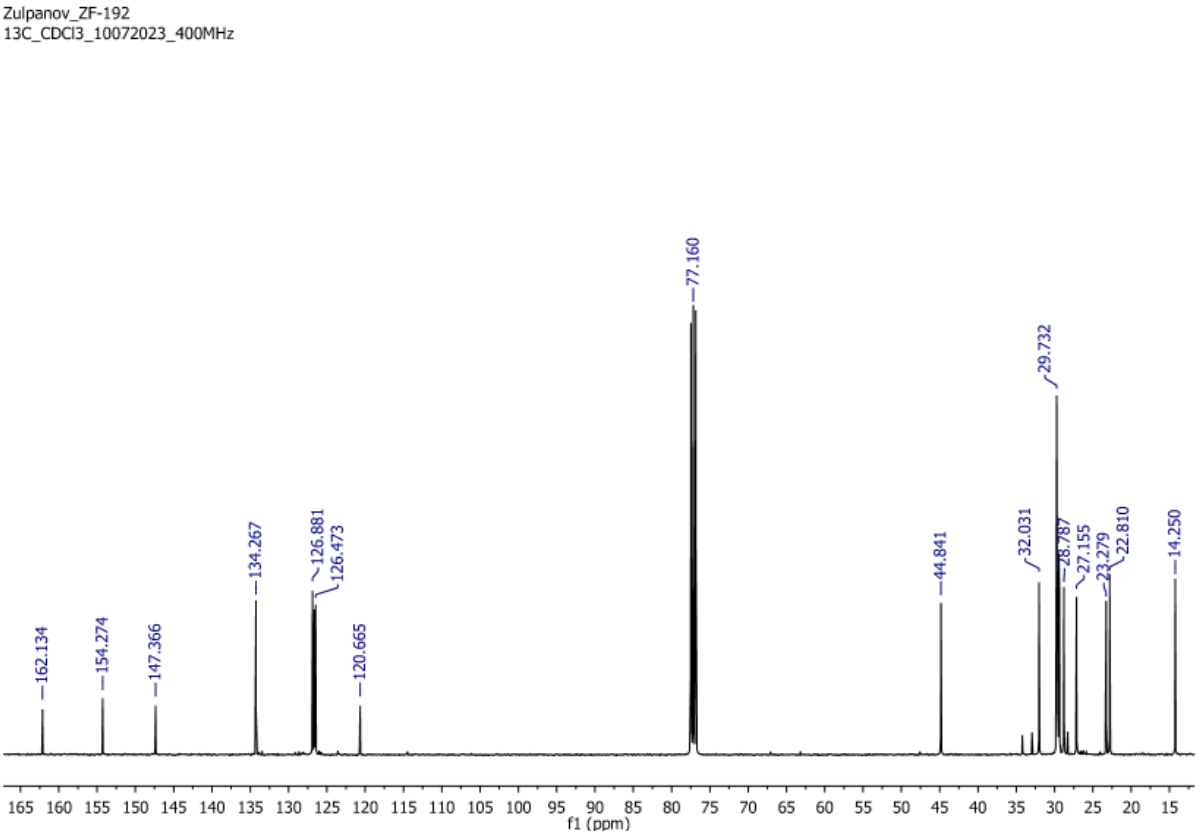


*Fig. 2. ^{13}C NMR spectrum of compound **9** in $CDCl_3$.*

The ratio of 2-methylquinazolin-4-one, alkyl halide and KOH in the ratio of 1:1.2 in the reagents involved in the reaction led to a relatively higher yield of the product. The reason for this can be explained by the shift of the equilibrium to the side of product formation due to the excess amount of alkyl halide. The reactivity of alkyl halides also depends on their structure. In particular, alkyl iodides react well with alkyl bromides and alkyl chlorides, resulting in higher yields of the products formed. Since the boiling point of methyl iodide and propyl chloride is lower than that of the solvent (alcohol) (method A), in order to avoid losses, the reactions are carried out in DMF solvent at a lower temperature (method B).

Table 1. Some physico-chemical parameters of compounds 1-9 synthesized in alcohol and DMF solution

№	Molecular formula	R_f	Melting point, °C	Yield, %
In ethanol				
1	$C_9H_8N_2O$	0.73	238-240	98
2	$C_{10}H_{10}N_2O$	0.57	103-105	27
3	$C_{11}H_{12}N_2O$	0.53	93-95	83
4	$C_{14}H_{18}N_2O$	0.68	65-67	83
5	$C_{14}H_{18}N_2O$	0.70	60-62	84
6	$C_{15}H_{20}N_2O$	0.65	59-60	80
7	$C_{16}H_{22}N_2O$	0.65	55-57	85
8	$C_{17}H_{24}N_2O$	0.63	55-57	86
9	$C_{21}H_{32}N_2O$	0.60	50-52	88
In DMFA				
2	$C_{10}H_{10}N_2O$	0,57	103-105	93

Table 2. IR spectra (ν, cm^{-1}) of 3-alkyl 2-methylquinazoline 4-ones (1-9)

№	C-N	CH	CH_2	C=O	C=N
1	1450	2979	2990	1669	1609
2	1478	2985	2925	1653	1598
3	1469	2993	2927	1656	1642
4	1469	2957	2925	1669	1572
5	1465	2955	2928	1671	1591
6	1471	2952	2925	1671	1590
7	1464	2951	2915	1677	1591
8	1461	2952	2914	1680	1590
9	1458	3061	2957	1661	1558

Conclusion. An improved method of quantitative yield synthesis of 2-methylquinazolin-4-one was developed by carrying out the heterocyclization reaction in the presence of thioacetamide and o-aminobenzoic acid. Synthesis of 3-alkyl-2-methylquinazolin-4-ones as a result of alkylation reactions of the obtained substance in the presence of alkylating agents of different structures was systematically studied. Such as 2-methyl-3-dodecylquinazolin-4-one, 2-methyl-3-octylquinazolin-4-one, 2-methyl-3-amylquinazolin-4-one, 2-methyl-3-isoamylquinazolin-4-one one the substance was synthesized anew. The obtained substances can be used as important synthons for further modifications. The structure of the obtained substances was analyzed and confirmed using modern physical research methods.

Acknowledgments. This work was supported by: Akad. S. Yu. Yunusov Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan. department of Organic synthesis.

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F. A. Zulpanov, A. R. Xurramov, X. M. Bobakulov, B. J. Elmuradov

3-ALKIL-2-METILXINAZOLIN-4-ON GOMOLOG LARINING SAMARALI SINTEZI

Referat. *Muammoning kelib chiqishi.* Kondersirlangan geterotsiklik birikmalar sintezi va biologik faolligini o'rganish natijasida yangi dorivor preparatlar ishlab chiqilmoqda, shu jumladan, 3-alkil-2-metilxinazolin-4-on hosilalari, ularning yangi biofaol hosilalarini aniqlandi. Ular asosida yangi dorivor preparatlar ishlab chiqarish dolzarb vazifalardan biri hisolanadi.

Ishning maqsadi. Geterosiklizatsiya reaksiyasi orqali dastlabki modda 2-metilxinazolin-4-onni qulay va samarali sintez usulini ishlab chiqish va ular asosida turli xil alkillovchi agentlar ishtirokida 3(H)almashingan-2-metilxinazolin-4-onlar sintezini amalga oshirish. Olingan moddalarning kimyoviy tuzilishlarini zamonaviy fizikaviy tadqiqot usullari IQ, ^{1}H va ^{13}C YaMR spektroskopiyasi yordamida aniqlash.

Metodologiya. 2-metilxinazolin-4-on asosida 3-alkil-2-metilxinazolin-4-onlaarni (2,3-dimetilxinazolin-4-on va boshqalar) sintez qilish, olingan moddalarning tuzilishlarini fizikaviy tadqiqot usullari: IQ, 1H ва 13C YaMR spektroskopiyasi spektrlari yordamida o'rganildi va reaktsiyalarning borishiga ta'sir etuvchi omillar tahlil qilindi.

Ilmiy yangilik. Geterosiklizatsiya reaksiyasining mutloq unumlarda 2-metilxinazolin-4-on sintez qilishning takomillashgan usuli ishlab chiqildi. Olingan modda asosida alkil birikmalarning yangi vakillari sintez qilindi.

Olingan natijalar. o-Aminobenzoy kislota bilan tioatsetamidning o'zaro reaksiyasi natijasida, yuqori unumlar bilan 2-metilxinazolin-4-onni samarali va qulay sintez usuli ishlab chiqildi hamda shu modda asosida 3-alkil-2-metilxinazolin-4-onlarni yangi hosilalari sintez qilindi. Olingan moddalarning tuzilishlari fizikaviy tadqiqot usullari yordamida o'rganildi, taklif etilgan tuzilishga mos ekanligi to'liq isbotlandi.

Kalit so'zlar: *o*-aminobenzoy kislota, tioatsetamid, halqalanish, alkilgalogenidlar, alkillash, 2-metilxinazolin-4-on, 3-alkil-2-metilxinazolin-4-onlar, IQ, ^{1}H va ^{13}C YaMR spektroskopiyasi.

Xususiyatlari:

- *o*-Aminobenzoy kislota va tioatsetamid ishtirokida geterosiklizatsiya reaksiyasi amalga oshirildi**.**
- 2-metilxinazolin-4-onni alkilgalogenidlar ishtirokida 3-alkil-2-metilxinazolin-4-onlar sintez qilindi.
- IQ, 1H va 13C YaMR spektroskopiya usullari yordamida ularning tuzilishlari tadqiq qilindi.

Ф. А. Зулпанов, А. Р. Хуррамов, Х. М. Бобакулов, Б. Ж. Эльмурадов

ЭФФЕКТИВНЫЙ СИНТЕЗ ГОМОЛОГОВ 3-АЛКИЛ-2-МЕТИЛХИНАЗОЛИН-4-ОНОВ

Реферат. *Предпосылки проблемы.* В результате изучения синтеза и биологической активности конденсированных гетероциклических соединений разработаны новые лекарственные препараты, в том числе производные 3-алкил-2-метилхиназолин-4-она, выявлены их биоактивные производные. Разработка новых лекарств на их основе актуальна.

Цель работы. Разработка метода синтеза исходных 2-метилхиназолин-4-онов реакцией гетероциклизации и на их основе синтеза 3(H)-замещенных 2-метилхиназолин-4-онов в присутствии алкилирующих агентов. Определение структур полученных веществ методами ИК, ^{1}H и ^{13}C ЯМР.

Методология. Синтезированы 3-алкил 2-метилхиназолин-4-онов на основе 2-метилхиназолин-4-она (2,3-диметилхиназолин-4-он и другие соединения, они исследованы физическими методами: ИК, ^{1}H и ^{13}C ЯМР, проанализированы факторы, влияющие на ход реакций.

Научная новизна. Разработан усовершенствованный метод синтеза 2-метилхиназолин-4-она с выходом по реакции гетероциклизации. Синтезированы новые представители алкильных соединений.

Полученные данные. Разработан метод синтеза 2-метилхиназолин-4-она с высокими выходами, синтезированы новые производные 3-алкил-2-метилхиназолин-4-онов на основу этого вещества. Строение их изучено физическими методами, доказано их соответствие предложенному строению.

Ключевые слова: о-аминобензойная кислота, тиоацетамид, циклизация, алкилгалогениды, алкилирование, 2-метилхиназолин 4-он, 3-алкил-2-метилхиназолин-4-он, ИК, ^{1}H и ^{13}C ЯМР.

Особенности:

- Гетероциклизация в присутствии о-аминобензойной кислоты, тиоацетамида.
- синтез 3-алкил-2-метилхиназолин-4-оны в присутствии 2-метилхиназолин-4-он алкил- галогенидов.
- исследовано строение методами спектроскопии ИК, ^{1}H и ^{13}C ЯМР.

UDC 541.49:577.164.186

F. R. JUMABAEV, S. A. PARDABOYEVA, M. D. ORIFJONOVA, M. SH. KARIMOV, A. T. SHARIPOV

COMPLEX OF LIPOIC ACID WITH CADMIUM(II): SYNTHESIS, HIRSHFELD SURFACE ANALYSIS AND MOLECULAR DOCKING STUDIES

Tashkent Pharmaceutical Institute, Tashkent, Uzbekistan.e-mail: farhodjumaboyev1@gmail.com

Admission date 27.02.2024

Abstract. *Background.* Drugs based on metal complexes are used in cancer chemotherapy. Cadmium complexes have been shown to limit the proliferation of cancer cells.

Purpose. Synthesis and study of complexes based on lipoic acid (LA) and cadmium (II) salts, molecular docking analysis.

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Подписано в печать 22.04.2024