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# THE ALKYLATION REACTION OF AROMATIC ACIDSHYDRAZIDES WITH (±)-CIS-3-DICHLOROMETHYL-1,2,2-TRIMETHYLCYCLOPENTAN-CARBOXYLIC ACID

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**Key words:** (±)-cis-3-dichloromethyl-1,2,2-trimethylcyclopentancarboxylic acid; hydrazides; hydrazones; alkylation

The article describes the study of the alkylation reaction of aromatic acids hydrazides with (±)-cis-3-dichloromethyl-1,2,2-trimethylcyclopentancarboxylic acid. The acid mentioned is a new substance obtained by oxidative cleavage of racemic camphor in the tetrachloromethane medium according to the method described earlier and modified by us. As a result of alkylation of aromatic acids hydrazides, a series of 3-[[2-(R-carbonyl)hydrazinylidene]methyl]-1,2,2-trimethylcyclopentancarboxylic acids has been obtained with the yields of 77-88%. According to the data of <sup>1</sup>H NMR spectra almost all products are E-isomers. The reaction of alkylation of anthranilic hydrazide proceeds with formation of the 1,2,3,4-tetrahydroquinazolin-4-one cycle and obtaining of (±)-cis-3-(3-amino-1,2,3,4-tetrahydroquinazolin-4-on-2-yl)-1,2,2-trimethylcyclopentancarboxylic acid. The composition of the compounds synthesized has been proven by elemental analysis, and their structure has been confirmed by <sup>1</sup>H NMR spectroscopy. According to the results of PASS prediction the compounds synthesized are potential diuretic, antiviral and antibacterial agents. The synthetic studies conducted show the possibility of using (±)-cis-3-dichloromethyl-1,2,2-trimethylcyclopentancarboxylic acid as a building block for extension of a number of biologically active substances synthesized in our previous studies on the basis of (±)-cis-1,2,2-trimethylcyclopentane-1,3-dicarboxylic (camphoric) acid.

## ДОСЛІДЖЕННЯ РЕАКЦІЇ АЛКІЛУВАННЯ ГІДРАЗИДІВ АРОМАТИЧНИХ КИСЛОТ (±)-ЦИС-3-ДИХЛОРОМЕТИЛ-1,2,2-ТРИМЕТИЛЦИКЛОПЕНТАНКАРБОНОВОЮ КИСЛОТОЮ

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**Ключові слова:** (±)-цис-3-дихлорометил-1,2,2-триметилциклопентанкарбонова кислота; гідразиди; гідразони; алкілування

Роботу присвячено дослідженню реакції алкілування гідразидів ароматичних кислот (±)-цис-3-дихлорометил-1,2,2-триметилциклопентанкарбоною кислотою. Зазначена кислота є новою сполукою, яку ми отримали окисним розщепленням рацемічної камфори у середовищі тетрахлорометану за методикою, описаною в літературі і модифікованою нами. У результаті алкілування гідразидів ароматичних кислот нами отримано ряд (±)-цис-3-[[2-(R-карбоніл)гідразиніліден]метил]-1,2,2-триметилциклопентанкарбонових кислот з виходом 77-88%. За даними спектрів <sup>1</sup>H ЯМР встановлено, що практично всі продукти є E-ізомерами. Реакція алкілування антранілового гідразиду перебігає із замиканням 1,2,3,4-тетрагідрохіназолін-4-онового циклу та утворенням (±)-цис-3-(3-аміно-1,2,3,4-тетрагідрохіназолін-4-он-2-іл)-1,2,2-триметилциклопентанкарбоною кислоти. Склад синтезованих речовин доведений елементним аналізом, а будова підтверджена методом <sup>1</sup>H ЯМР-спектроскопії. За результатами віртуального прогнозу PASS синтезовані сполуки є потенційними діуретичними, антивірусними та антибактеріальними засобами. Проведені синтетичні дослідження показують можливість використання (±)-цис-3-дихлорометил-1,2,2-триметилциклопентанкарбоною кислоти як білдінг блоку для розширення ряду біологічно активних речовин, синтезованих нами у попередніх дослідженнях на основі (±)-цис-1,2,2-триметилциклопентан-1,3-дикарбоною (камфорної) кислоти.

## ИССЛЕДОВАНИЕ РЕАКЦИИ АЛКИЛИРОВАНИЯ ГИДРАЗИДОВ АРОМАТИЧЕСКИХ КИСЛОТ (±)-ЦИС-3-ДИХЛОРОМЕТИЛ-1,2,2-ТРИМЕТИЛЦИКЛОПЕНТАНКАРБОНОВОЙ КИСЛОТОЙ

**Е.А.Цапко**  
**Ключевые слова:** (±)-цис-3-дихлорметил-1,2,2-триметилциклопентанкарбоновая кислота; гидразиды; гидразоны; алкилирование

Работа посвящена исследованию реакции алкилирования гидразидов ароматических кислот (±)-цис-3-дихлорметил-1,2,2-триметилциклопентанкарбоновой кислотой. Указанная кислота является новым соединением, которое мы получили окислительным расщеплением рацемической камфори в среде тетрахлорометана по методике, описанной в литературе и модифицированной нами. В результате алкилирования гидразидов ароматических кислот нами получен ряд (±)-цис-3-[[2-(R-карбонил)гидразинилиден]метил]-1,2,2-триметилциклопентанкарбоновых кислот с выходом 77-88%. По данным спектров <sup>1</sup>H ЯМР установлено, что практически все продукты являются E-изомерами. Реакция алкилирования антранилового гидразида протекает с замыканием 1,2,3,4-тетрагидрохиноазолин-4-онового цикла и образованием (±)-цис-3-(3-амино-1,2,3,4-тетрагидрохиноазолин-4-он-2-ил)-1,2,2-триметилциклопентанкарбоновой кислоты. Состав синтезированных веществ доказан элементным анализом, а строение подтверждено методом <sup>1</sup>H ЯМР-спектроскопии. По результатам виртуального прогноза PASS синтезированные соединения являются потенциальными диуретическими, антивирусными и антибактериальными средствами. Проведенные синтетические исследования показывают возможность использования (±)-цис-3-дихлорметил-1,2,2-триметилциклопентанкарбоновой кислоты в качестве билдинг блока для расширения ряда биологически активных веществ, синтезированных нами в предыдущих исследованиях на основе (±)-цис-1,2,2-триметилциклопентан-1,3-дикарбоновой (камфорной) кислоты.

In previous studies we identified derivatives of ( $\pm$ )-*cis*-1,2,2-trimethylcyclopentan-1,3-dicarboxylic (camphoric acid) with the hypoglycemic [1], anti-convulsant [2], diuretic [3] activity. In order to develop new approaches to the synthesis of this series we have obtained 3-dichloromethyl-1,2,2-trimethylcyclopentancarboxylic acid (compound **1**, Scheme 1). Acid **1** and camphoric acid contain the same moiety of 1,2,2-trimethylcyclopentancarboxylic acid.

Acid **1** was obtained by oxidative cleavage of camphor under the action of alkali in the presence of *tert*-butanol in the carbon tetrachloride medium (Scheme 1). For the first time the synthesis of *d*-isomer of acid **1** from *d*-camphor was described by Meyers et al. [4, 5], but the spectral characteristics of the acid were not given, and only chlorolactone was described among its derivatives. We have reproduced and optimized this method for racemic camphor. When carrying out the synthesis we excluded the stages of the solvent stripping and extraction of the product with diethyl ether, as well as reduced the number of *tert*-butanol used. As a result, ( $\pm$ )-acid **1** with the yield of 70% has been obtained, and it coincides with the results of authors [5].

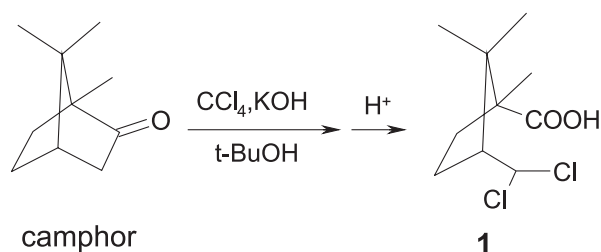
Compound **1** is a white crystalline substance that dissolves in aqueous solutions of alkali and most organic solvents. In  $^1\text{H}$  NMR spectrum of acid **1** the characteristic group of signals of the 1,2,2-trimethylcyclopentan fragment is present, the signal of the dichloromethyl group proton is observed as a doublet at

6.19 ppm. The mass spectrum of this compound does not have signals of a molecular ion. The heaviest ion has  $m/z$  – 167. It is probably formed by cleavage of HCl with the lactone cycle closure and the subsequent cleavage of another chlorine atom.

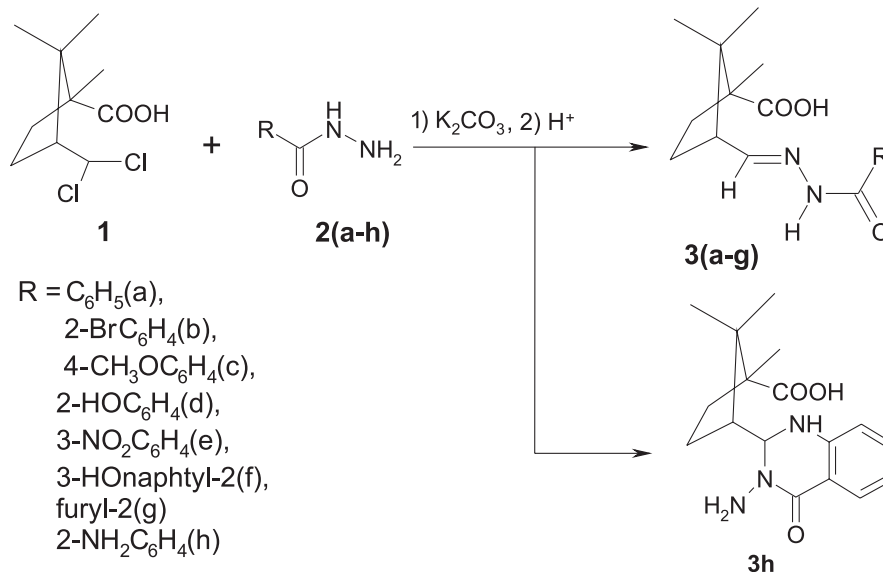
There are almost no data published on the use of dichloromethyl aliphatic derivatives in the preparative organic synthesis. This fact can be explained by insufficient accessibility and low reactivity of these derivatives. Only the compounds with an activated dichloromethyl group, such as dichloromethyl ether [6] and dichloromethylphenylsulfoxide [7], were used.

The study of the dichloromethyl group reactivity of compound **1** was started from the alkylation reaction of aromatic acids hydrazides **2** (Scheme 2). The reaction was carried out in the aqueous-alcoholic solution in the presence of potassium carbonate. As a result, a series of 3-{[2-(*R*-carbonyl)hydrazinylidene]methyl}-1,2,2-trimethylcyclopentancarboxylic acids **3a-g** (Scheme 2) with preparative yields was obtained. All acids **3a-g** obtained are colourless crystalline compounds that are soluble in most organic solvents and practically insoluble in water. Proton signals of the expected structural fragments with the corresponding intensity and multiplicity were observed in  $^1\text{H}$  NMR spectra of acids **3a-g**, the chemical shift of the azometine group proton was about 7.7 ppm. The proton signal of the NH-group of compounds **3a-g** was observed as one singlet, indicating that the products consisted of a single geometric isomer. The exception is acid **3b** with the volumetric substituent – bromine in the *ortho*-position to the hydrazide group. The integrated intensity of two singlets of NH protons belonging to *E*- and *Z*- isomers of acid **3b** is in the ratio of 2:1.

The geometric configuration of compounds **3a-g** was determined on the example of acid **4c** using the homonuclear Overhauser effect [8]. In Fig. the  $^1\text{H}$  NMR spectrum of this compound is saturation of the signal of N=CH proton. As it can be seen, the singlet of



Scheme 1



Scheme 2

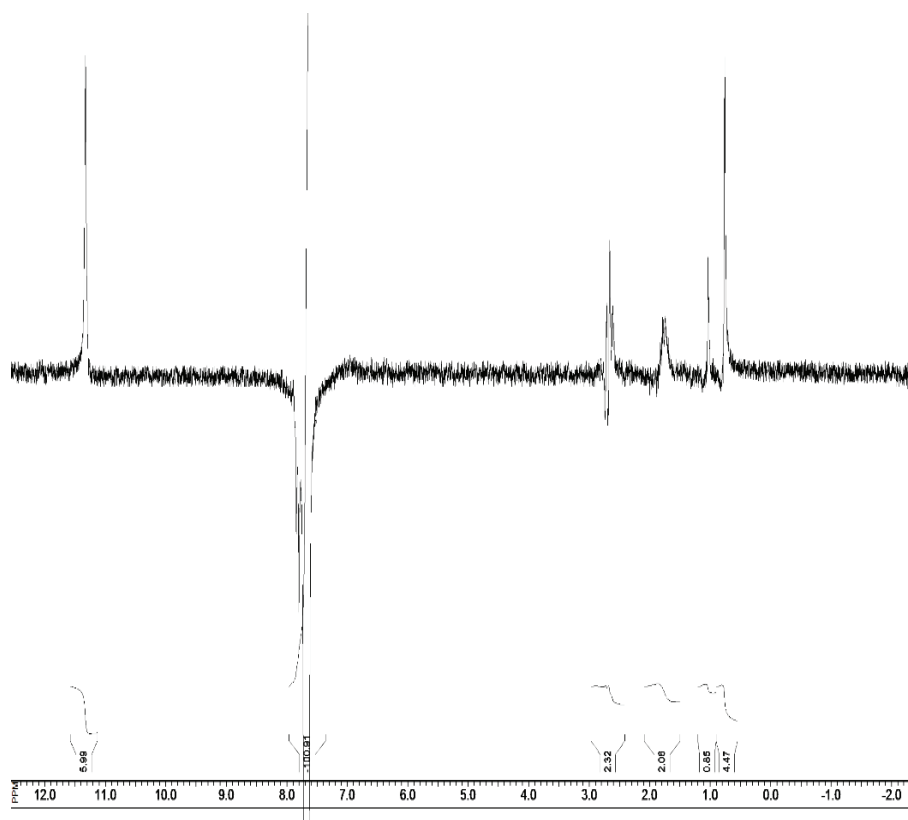


Fig. The  $^1\text{H}$  NMR spectrum of ( $\pm$ )-*cis*-3-[(*E*)-2-[(4-methoxybenzoyl)hydrazineylidene]methyl]-1,2,2-trimethylcyclopentanecarboxylic acid **3c** with saturation of the signal at 7.76 ppm.

the nearest NH proton (11.32 ppm) is characterized by the biggest integrated intensity indicating *E*-configuration of the compound studied. Four other signals belong to protons of CH, CH<sub>2</sub> and two CH<sub>3</sub> groups. It is obvious that for compounds **3(a-g)** *E*-configuration is more favourable than *Z*-configuration since the cyclopentane fragment together with the carboxyl group can create steric hindrance for *Z*-configuration.

The result of the reaction between acid **1** and anthranilic hydrazide **2h** was different from products **3a-g** previously discussed (Scheme 2). The product of the reaction was identified as ( $\pm$ )-*cis*-3-(3-amino-1,2,3,4-tetrahydroquinazolin-4-on-2-yl)-1,2,2-trimethylcyclopentanecarboxylic acid (compound **3h**). The signals of proton of NH-N=C group were not observed in the  $^1\text{H}$  NMR spectrum of acid **3h**, while signals of the amino group and the 1,2,3,4-tetrahydroquinazolin-4-one moiety were present.

The PASS virtual screening [9] for compounds **3(a-g)** was conducted. Among the aforementioned types of the biological activity studied for derivatives of camphor acid the diuretic activity is predicted for compounds **3(a-g)** with the index  $P_a$  in the range of 0.40-0.55. The anticonvulsant action ( $P_a = 0.5-0.6$ ) is expected for compound **3h** and its virtual *N*-acyl derivatives. The cytoprotective and antiviral activities have the highest values of  $P_a$  (~0.7) for compounds **3(a-g)**, whereas analysis of the literature data shows that hydrazones have antibacterial [10], antiprotozoal [11] and fungicidal [12, 13] properties.

## Experimental Part

According to the homonuclear Overhauser effect experiment the  $^1\text{H}$  NMR spectra were recorded on a Varian Mercury VX-200 (200 MHz) spectrometer, the solvent was DMSO-*d*<sub>6</sub> with TMS as an internal standard. The mass spectra were obtained on a Varian 1200L spectrometer in full scanning mode in the range of 35-700 *m/z* and EI at 70 eV. Elemental analysis was performed on an EuroVector EA-3000 microanalyzer. Melting points were determined on a Kofler bench. The purity of the compounds synthesized was confirmed by TLC using Silufol UV<sub>254</sub> plates and the ethyl acetate – chloroform system (3:2 v/v) as an eluent.

**(±)-*Cis*-3-dichloromethyl-1,2,2-trimethylcyclopentanecarboxylic acid (1)**. To the solution of 3 g (0.02 Mol) of camphor in 30 ml of tetrachloromethane add 26 g (0.46 Mol) of a freshly crushed potassium hydroxide. To the obtained mixture add 4 ml of *tert*-butanol and stir. Upon completion of the exothermic reaction stirring was continued for 40 min at 70°C. Cool the mixture and extract potassium salt of acid **1** by three portions of water with 50 ml each. Combine aqueous extracts and acidify them with a dilute sulfuric acid. Filter a white precipitate formed and recrystallize from aqueous ethanol. The yield is 70%. M.p. – 154-155°C. C<sub>10</sub>H<sub>16</sub>Cl<sub>2</sub>O<sub>2</sub>.  $^1\text{H}$  NMR,  $\delta$ , ppm: 0.80c (3H, CH<sub>3</sub>), 1.08c (3H, CH<sub>3</sub>), 1.19c (3H, CH<sub>3</sub>), 1.23-1.40m, 1.55-1.72m, 1.81-2.02m, 2.14-2.35m (4H, CH<sub>2</sub>CH<sub>2</sub>), 2.44-2.62m (1H, CH), 6.19d (1H, CHCl<sub>2</sub>, *J* = 8 Hz), 12.08s

(1H, COOH). IE-MS,  $m/z(I_{rel}, \%)$ : 167(25), 121(100), 116(35), 109(34), 87(56), 83(51), 81(41).

**The general procedure for the synthesis of ( $\pm$ )-*cis*-3-[(2-(*R*-carbonyl)hydrazinylidene)methyl]-1,2,2-trimethylcyclopentanecarboxylic acids (3).** Dissolve 2.4 g (0.01 Mol) of acid 1 and 1.2 g (0.01 Mol) of potassium carbonate in 8 ml of 20% ethanol, add 0.011 Mol of the corresponding hydrazide 2 and heat under the reflux for 2 h. Cool the solution, acidify with a dilute sulfuric acid. Filter the precipitate formed and recrystallize from aqueous ethanol.

**( $\pm$ )-*Cis*-3-{(E)-[(2-benzoyl)hydrazinylidene]methyl}-1,2,2-trimethylcyclopentanecarboxylic acid (3a).** The yield is 88%. M.p. – 202-203°C. Found, %: C 67.61, H 7.29, N 9.39.  $C_{17}H_{22}N_2O_3$ . Calculated, %: C 67.53, H 7.33, N 9.26.  $^1H$  NMR,  $\delta$ , ppm: 0.77c (3H,  $CH_3$ ), 1.05c (3H,  $CH_3$ ), 1.15c (3H,  $CH_3$ ), 1.33-1.51m (1H,  $CH_2CH_2$ ), 1.68-1.86m (2H,  $CH_2CH_2$ ), 2.34-2.45m (1H,  $CH_2CH_2$ ), 2.62-2.79m (1H, CH), 7.40-7.56m (3H, H-3,4,5), 7.69d (1H,  $CH=N$ ,  $J=4$  Hz), 7.85d (2H, H-2,6,  $J=4$  Hz), 11.44s (1H, NH), 12.16bs (1H, COOH).

**( $\pm$ )-*Cis*-3-{2-[(2-bromobenzoyl)hydrazinylidene]methyl}-1,2,2-trimethylcyclopentanecarboxylic acid (3b).** The yield is 87%. M.p. – 244-245°C. Found, %: C 53.44, H 5.59, N 7.46.  $C_{17}H_{21}BrN_2O_3$ . Calculated, %: C 53.55, H 5.51, N 7.35.  $^1H$  NMR,  $\delta$ , ppm: 0.71c (3H,  $CH_3$ ), 1.03c (3H,  $CH_3$ ), 1.15c (3H,  $CH_3$ ), 1.33-1.47m (1H,  $CH_2CH_2$ ), 1.56-1.62m (1H,  $CH_2CH_2$ ), 1.70-1.85m (1H,  $CH_2CH_2$ ), 2.29-2.43m (1H,  $CH_2CH_2$ ), 2.63-2.78m (1H, CH), 7.26-7.69m (5H,  $C_6H_4+CH=N$ ), 11.54s (1H, NH), 12.14bs (1H, COOH).

**( $\pm$ )-*Cis*-3-{(E)-2-[(4-methoxybenzoyl)hydrazinylidene]methyl}-1,2,2-trimethylcyclopentanecarboxylic acid (3c).** The yield is 87%. M.p. – 157-158°C. Found, %: C 65.00, H 7.33, N 8.52.  $C_{18}H_{24}N_2O_4$ . Calculated, %: C 65.04, H 7.28, N 8.43.  $^1H$  NMR,  $\delta$ , ppm: 0.77c (3H,  $CH_3$ ), 1.03c (3H,  $CH_3$ ), 1.15c (3H,  $CH_3$ ), 1.33-1.50m (1H,  $CH_2CH_2$ ), 1.67-1.85m (2H,  $CH_2CH_2$ ), 2.34-2.45m (1H,  $CH_2CH_2$ ), 2.60-2.77m (1H, CH), 3.80s (3H,  $CH_3O$ ), 7.00d (2H, H-3,5,  $J=12$  Hz), 7.67d (1H,  $CH=N$ ,  $J=8$  Hz), 7.82d (2H, H-2,6,  $J=12$  Hz), 11.32s (1H, NH), 12.14bs (1H, COOH).

**( $\pm$ )-*Cis*-3-{(E)-2-[(2-hydroxybenzoyl)hydrazinylidene]methyl}-1,2,2-trimethylcyclopentanecarboxylic acid (3d).** The yield is 77%. M.p. – 172-173°C. Found, %: C 64.15, H 7.03, N 9.01.  $C_{17}H_{22}N_2O_4$ . Calculated, %: C 64.13, H 6.97, N 8.80.  $^1H$  NMR,  $\delta$ , ppm: 0.78c (3H,  $CH_3$ ), 1.06c (3H,  $CH_3$ ), 1.15c (3H,  $CH_3$ ), 1.34-1.51m (1H,  $CH_2CH_2$ ), 1.70-1.89m (2H,  $CH_2CH_2$ ), 2.34-2.46m (1H,  $CH_2CH_2$ ), 2.64-2.80m (1H, CH), 6.84-6.96m (2H, H-5+ $CH=N$ ), 7.40t (1H, H-4,  $J=8$ Hz) 7.72d (1H, H-3,  $J=8$  Hz), 7.82d (1H, H-6,  $J=8$  Hz), 9.03s (1H, OH) 11.54s (1H, NH), 12.02bs (1H, COOH).

**( $\pm$ )-*Cis*-3-{(E)-2-[(3-nitrobenzoyl)hydrazinylidene]methyl}-1,2,2-trimethylcyclopentanecarboxylic acid (3e).** The yield is 86%. M.p. – 188-189°C. Found, %: C 58.84, H 6.16, N 12.19.  $C_{17}H_{21}N_3O_5$ .

Calculated, %: C 58.78, H 6.09, N 12.10.  $^1H$  NMR,  $\delta$ , ppm: 0.79c (3H,  $CH_3$ ), 1.05c (3H,  $CH_3$ ), 1.15c (3H,  $CH_3$ ), 1.32-1.53m (1H,  $CH_2CH_2$ ), 1.69-1.92m (2H,  $CH_2CH_2$ ), 2.30-2.45m (1H,  $CH_2CH_2$ ), 2.64-2.84m (1H, CH), 7.68-7.88m (2H, H-3+ $CH=N$ ), 8.29d (1H, H-2,  $J=8$  Hz), 8.39d (1H, H-4,  $J=8$  Hz), 8.69s (1H, H-6), 11.78s (1H, NH), 12.16bs (1H, COOH).

**( $\pm$ )-*Cis*-3-{(E)-2-[(3-hydroxynaphthalen-2-ylcarbonyl)hydrazinylidene]methyl}-1,2,2-trimethylcyclopentanecarboxylic acid (3f).** The yield is 71%. M.p. – 229-230°C. Found, %: C 68.44, H 6.55, N 7.69.  $C_{21}H_{24}N_2O_4$ . Calculated, %: C 68.46, H 6.57, N 7.60.  $^1H$  NMR,  $\delta$ , ppm: 0.79c (3H,  $CH_3$ ), 1.07c (3H,  $CH_3$ ), 1.17c (3H,  $CH_3$ ), 1.25-1.50m (2H,  $CH_2CH_2$ ), 1.74-1.89m (2H,  $CH_2CH_2$ ), 2.70-2.85m (1H, CH), 7.31-7.87m (7H,  $CH=N$ +naphthyl), 8.39s (1H, OH), 11.68s (1H, NH), 12.16bs (1H, COOH).

**( $\pm$ )-*Cis*-3-{2-[(furyl-2-ylcarbonyl)hydrazinylidene]methyl}-1,2,2-trimethylcyclopentanecarboxylic acid (3g).** The yield is 88%. M.p. – 203-204°C. Found, %: C 61.61, H 6.96, N 9.70.  $C_{15}H_{20}N_2O_4$ . Calculated, %: C 61.63, H 6.90, N 9.58.  $^1H$  NMR,  $\delta$ , ppm: 0.75c (3H,  $CH_3$ ), 1.04c (3H,  $CH_3$ ), 1.14c (3H,  $CH_3$ ), 1.68-1.90m (2H,  $CH_2CH_2$ ), 1.29-1.50m, 2.29-2.51m (2H,  $CH_2CH_2$ ), 2.70-2.85m (1H, CH), 6.62-6.66m (1H, H-4), 7.17-7.22m (1H, H-3), 7.65-7.71m (1H,  $CH=N$ ), 7.86-7.89m (1H, H-5), 11.42s (1H, NH), 12.16bs (1H, COOH).

**( $\pm$ )-*Cis*-3-(3-amino-1,2,3,4-tetrahydroquinazolin-4-on-2-yl)-1,2,2-trimethylcyclopentanecarboxylic acid (3h).** The yield is 47%. M.p. – 159-160°C. Found, %: C 64.39, H 7.28, N 13.28.  $C_{17}H_{23}N_3O_3$ . Calculated, %: C 64.33, H 7.30, N 13.24.  $^1H$  NMR,  $\delta$ , ppm: 0.86c (3H,  $CH_3$ ), 0.88c (3H,  $CH_3$ ), 1.01c (3H,  $CH_3$ ), 1.13-1.32m, 1.48-1.70m, 1.76-1.99m (3H,  $CH_2CH_2$ ), 2.20-2.43m (2H,  $CH_2CH_2$ ), 4.68dd (1H, NH,  $J=8$  Hz, 4Hz) 4.86s (2H,  $NH_2$ ), 6.61-6.71m (2H, H-2,6,  $J=8$  Hz), 6.93d (1H, H-8,  $J=4$  Hz), 7.22t (1H, H-7,  $J=8$  Hz), 7.58d (1H, H-5,  $J=8$  Hz), 12.16bs (1H, COOH).

## Conclusions

1. The synthesis of ( $\pm$ )-*cis*-3-dichloromethyl-1,2,2-trimethylcyclopentanecarboxylic acid has been carried out, and its structure has been confirmed by the methods of  $^1H$  NMR spectroscopy and mass spectrometry.

2. As a result of the alkylation reaction of aromatic acids hydrazides with ( $\pm$ )-*cis*-3-dichloromethyl-1,2,2-trimethylcyclopentanecarboxylic acid a number of the corresponding hydrazones has been obtained. Almost all acids are E-isomers, and it has been confirmed by  $^1H$  NMR spectroscopy.

3. It has been found that the alkylation reaction of anthranilic hydrazide with ( $\pm$ )-*cis*-3-dichloromethyl-1,2,2-trimethylcyclopentanecarboxylic acid completes with formation of the 1,2,3,4-tetrahydroquinazolin-4-one cycle and obtaining of ( $\pm$ )-*cis*-3-(3-amino-1,2,3,4-tetrahydroquinazolin-4-on-2-yl)-1,2,2-trimethylcyclopentanecarboxylic acid.

**References**

1. Tsapko Ye. O., Grytsenko I. S., Maloshtan L. M., Tymoshina I. O., Sytnik K. M., Yakovleva L. V., Shapoval O. M. *Current issues of pharmaceutical and medical science and practice*, 2013, Vol. 13, No.3, pp.106-108.
2. Tsapko Ye. O., Grytsenko I. S., Samura B. A., Nikolaev V. O. *Medicines to human: modern problems of creation and testing of drugs: materials XXV jubilee scientific and practical conference, Kharkov, 2008*, pp.388-393.
3. Tsapko Ye. O., Grytsenko I. S., Krasilnikova O. A., Bushlya N. E. *Visnyk farmaciyi – Bulletin of pharmacy*, 2007, No.3(51), pp.12-17.
4. Meyers C. Y., Kolb V. M. *J. Org. Chem.*, 1978, Vol. 43, No.10, pp.1985-1990.
5. Pat. US 3896164. – Publ. 22.07.75.
6. García O., Nicolás E., Albericio F. *Tetrahedron Lett.*, 1983, Vol. 44, No.27, pp.4961-4963, doi:10.1016/S0040-4039(03)01168-7.
7. Reutrakul V., Herunsalee K. *Tetrahedron Lett.* 1983, Vol. 24, No.5, pp.527-530, doi:10.1016/S0040-4039(00)81455-0.
8. Claridge T. D. W. *High-resolution NMR Techniques in Organic Chemistry*. Newnes, 2009, 383 p.
9. [www.pharmaexpert.ru/passonline/index.php](http://www.pharmaexpert.ru/passonline/index.php).
10. Sesaiah K. S., Muniyandy S., Atmakuru R. *Eur. J. Med. Chem.*, 2001, Vol. 36, No.7-8, pp.615-625, doi: 10.1016/S0223-5234(01)01255-7.
11. Inam A., Siddiqui S. M., Macedo T. S., Moreira D. R. M., Leite A. C. L., Soares M. B. P., Azam A. *Eur. J. Med. Chem.*, 2014, Vol.75, pp.67-76.
12. Backes G. L., Neumann D. M., Jursic B. S. *Bioorg. Med. Chem.*, 2014, in Press, doi: 10.1016/j.bmc.2014.07.022.
13. Neumann D. M., Cammarata A., Backes G., Palmer G. E., Jursic B. S. *Bioorg. Med. Chem.*, 2014, Vol. 22, No.2, pp.813-826, doi: 10.1016/j.bmc.2013.12.010.

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