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# SYNTHESIS OF 2-R-2-(1-ARYL-7,8-DIMETHOXY-5*H*-2,3-BENZODIAZEPIN-4-YL)ACETIC ACID ESTERS IN THE ESCHENMOSER REACTION

**E. S. Sizonenko[1]*, I. K. Kobrakov[2], V. Yu. Popov[1], S. Yu. Suikov[1], and S. L. Bogza[1]**

*A method for the synthesis of 2-R-2-(1-aryl-7,8-dimethoxy-5H-2,3-benzodiazepin-4-yl)acetic acid esters from 2-R-2-(1-aryl-7,8-dimethoxy-5H-2,3-benzodiazepin-4-ylsulfanyl)acetic acid esters through Eschenmoser reaction has been developed.*

**Keywords:** 5*H*-2,3-benzodiazepine, triethyl phosphite, Eschenmoser reaction, functionalization, sulfide contraction.

5*H*-Benzodiazepine derivatives were first obtained about 50 years ago and its core practically never found in nature, however occupied the position of a promising subject in medicinal chemistry for the construction of a new generation anxiolytic and nootropic agents [1]. However, the ability of these compounds to contract the seven-membered ring in the presence of acids [2, 3] significantly limits the range of synthetic applications. Progress in the chemistry of 5*H*-2,3-benzodiazepines in recent years is based on conversions of their 4- and 1-thioxo derivatives, for annelation of heterocyclic nuclei to the diazepine ring [4, 5]. Up until now the chemistry of 5*H*-2,3-benzodiazepines has led to the formation of carbon–heteroatom bonds, which markedly depletes the spectrum of products available and, correspondingly, the spectrum of possible types of biological activity. The formation of carbon–carbon bonds should be the challenge of organic chemistry in the synthesis and modifications of 5*H*-2,3-benzodiazepines.

In our opinion, one of the most interesting of the current methods for forming carbon–carbon bonds is the Eschenmoser reaction, known also as "sulfide contraction", described for the first time by Knott [6]. The Eschenmoser reaction involves formation of β-enaminocarbonyl derivatives **3** from *C*-(2-oxoalkyl)-substituted thioamides and thiolactams **1** by the elimination of the sulfur atom from episulfide intermediate **2** by thiaphilic reagents – strong bases and/or trivalent phosphorus derivatives [7-11].

This reaction was used effectively for the first time in the synthesis of vitamin $B_{12}$ [7, 8]. Eschenmoser showed the scope of this conversion in the example of the condensation of pyrrolidine-2-thione with

*To whom correspondence should be addressed, e-mail: esizonenko@i.ua.

[1]L. M. Litvinenko Institute of Physical Organic Chemistry and Coal Chemistry, National Academy of Sciences of Ukraine, 70 R. Luxemburg St., Donetsk 83114, Ukraine.
[2]I. M. Gubkin Russian State University of Oil and Gas, 65 Leninsky Ave., Moscow 119991, Russia; e-mail: ikobrakov@mail.ru.

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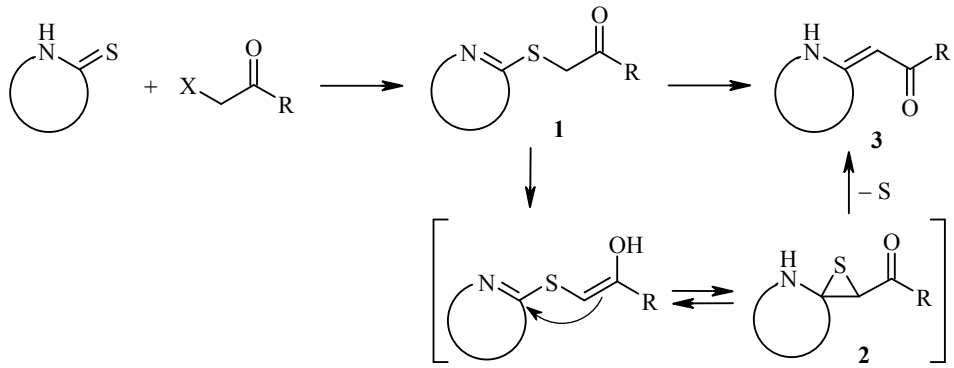
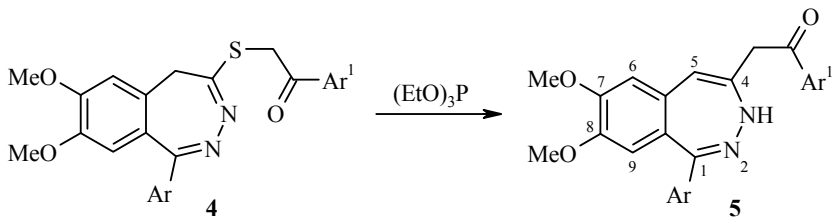


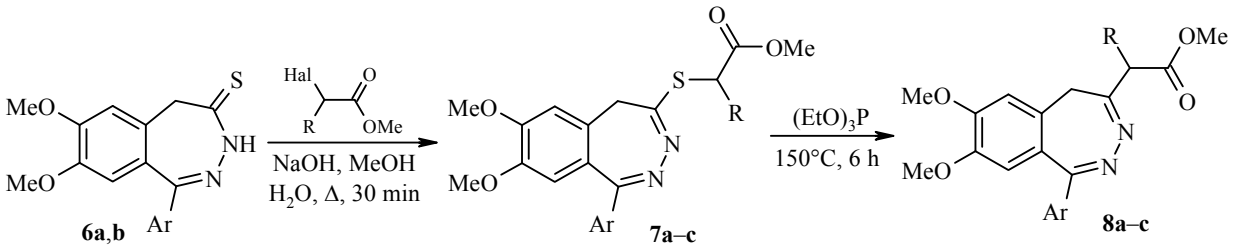
bromomethyl ketones and 2-halocarboxylic acid esters, with the formation of the corresponding vinylogs of amides and urethanes. The Eschenmoser reaction has a series of advantages as an alternative route for the formation of a carbon–carbon bond; the reaction conditions are fairly mild, reagents are inexpensive, and the process is highly selective. In addition, sulfur contraction does not affect the majority of functional groups and retains the configuration of the other fragments of the molecule. The area of application of the reaction was broadened significantly with the use of universal thiaphilic reagents, the trialkyl phosphites [9]. It has been applied widely in the synthesis of 2-oxoalkyl derivatives of nitrogen heterocycles with a various ring size. The Eschenmoser reaction was employed in the total syntheses of natural compounds, alkaloids, such as pumiliotoxin S, gephyrotoxin [10], allosedamine [11], and many others.

In a previous publication [12], we investigated the conversion of 4-phenacylsulfanyl derivatives of 5*H*-2,3-benzodiazepine **4** under Eschenmoser reaction conditions using triethyl phosphite as thiaphilic reagent. Sulfides **4** upon heating with triethyl phosphite are converted into ketones **5** in good yields. In the overwhelming majority of cases of Eschenmoser reaction the formed C=C bond is exocyclic. However in our case, it was established that the products of the conversion of keto sulfides **4** under the conditions of the Eschenmoser reaction are 2-(1-aryl-7,8-dimethoxy-3*H*-2,3-benzodiazepin-4-yl)-1-phenylethanones **5**, that was confirmed with the help of heteronuclear two-dimensional HCQC and HMBC experiments.



The introduction of readily modifiable groups, such as carboxyl, carbonyl, or amino, into the molecule significantly increases its biological potential. Consequently, the aim of the present work was the development of a method for the synthesis of carboxylic acids with a 2,3-benzodiazepine fragment as a general scheme, analogous to that described in study [12]. It was established that the alkylation of 1-aryl-7,8-dimethoxy-3,5-dihydro-2,3-benzodiazepine-4-thiones **6a**,**b** with the methyl esters of chloroacetic or 2-bromopropionic acids in methanol in the presence of alkali proceeds with the formation of the methyl esters of 2-R-2-(7,8-dimethoxy-1-phenyl-5*H*-2,3-benzodiazepin-4-ylsulfanyl)acetic acids **7a-c** in 65-75% yield, the structures of which were confirmed by IR and $^1$H NMR spectroscopy and by data of elemental analysis (Table 1).

Sulfides **7a-c** were converted upon heating with triethyl phosphite over 6 h into desired products which, according to data of elemental analysis, did not contain sulfur. The spectral characteristics of the final compounds **8a-c** confirmed their structure as the methyl esters of 2-R-2-(1-aryl-7,8-dimethoxy-5*H*-2,3-benzodiazepin-4-yl)acetic acids. When a chiral center was present in the exocyclic substituent (compounds




**6 a** Ar = Ph, **b** Ar = 4-$MeC_6H_4$; **7**, **8 a** Ar = Ph, R = H; **b** Ar = 4-$MeC_6H_4$, R = Me; **c** Ar = 4-$MeC_6H_4$, R = H; Hal = Br, Cl

**7b** and **8b**), both proton and carbon spectra were complicated by the doubling of sets of signals. The spectra were fairly complex due to the overlap of several signals and the presence of dynamic effects (the mobility of the diazepine ring was within the NMR time scale). A complete assignment of the signals in the spectrum was carried out using heteronuclear HCQC and HMBC correlations (Figs. 1 and 2).

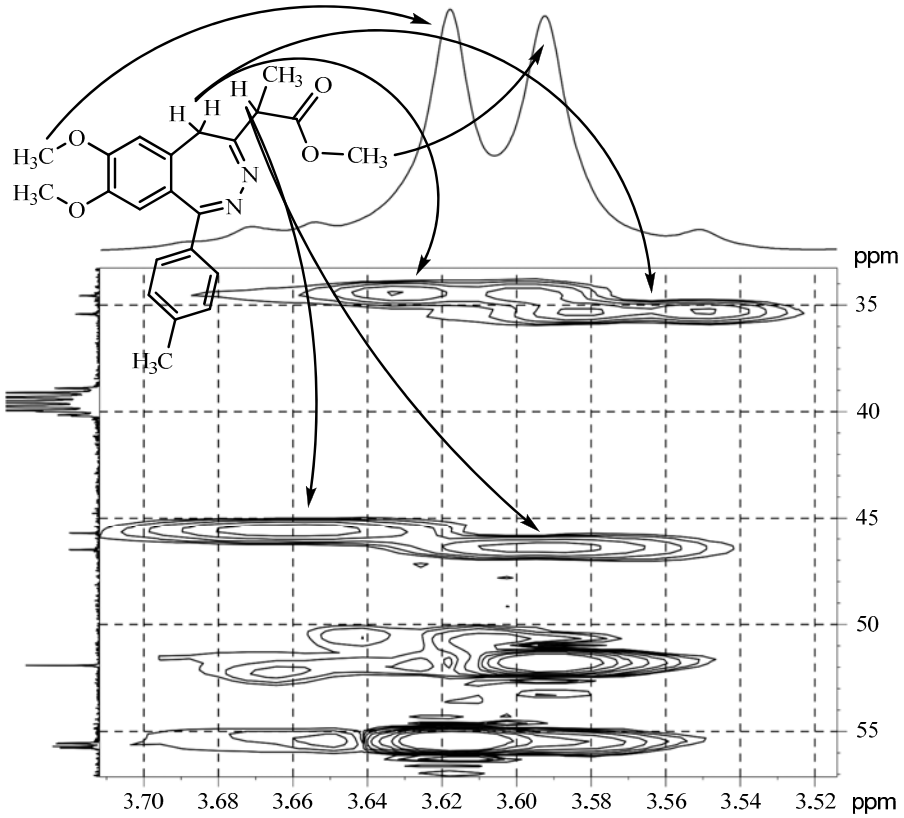



Fig. 1. Assignment of signals in the spectrum of compound **8b** using the HCQC procedure.

The downfield quartet signal in the $^1$H NMR spectrum of compound **8b** is masked completely by the more intense signals of the methyl groups, and the identification of its position without using the two-dimensional procedures was impossible. An analogous selective splitting of signals was observed in the $^{13}$C NMR spectrum. It should be mentioned that according to the HMBC data all these multiplexes are in the same structure and seemingly belong to optical isomers displayed in the spectrum as a result of the mutual influence of the overall chiral seven-membered ring and the asymmetric exocyclic tertiary carbon. The assignment of signals carried out enables unequivocal establishment of the position of the double bond, between atoms N(3) and C(4) of the diazepine ring.

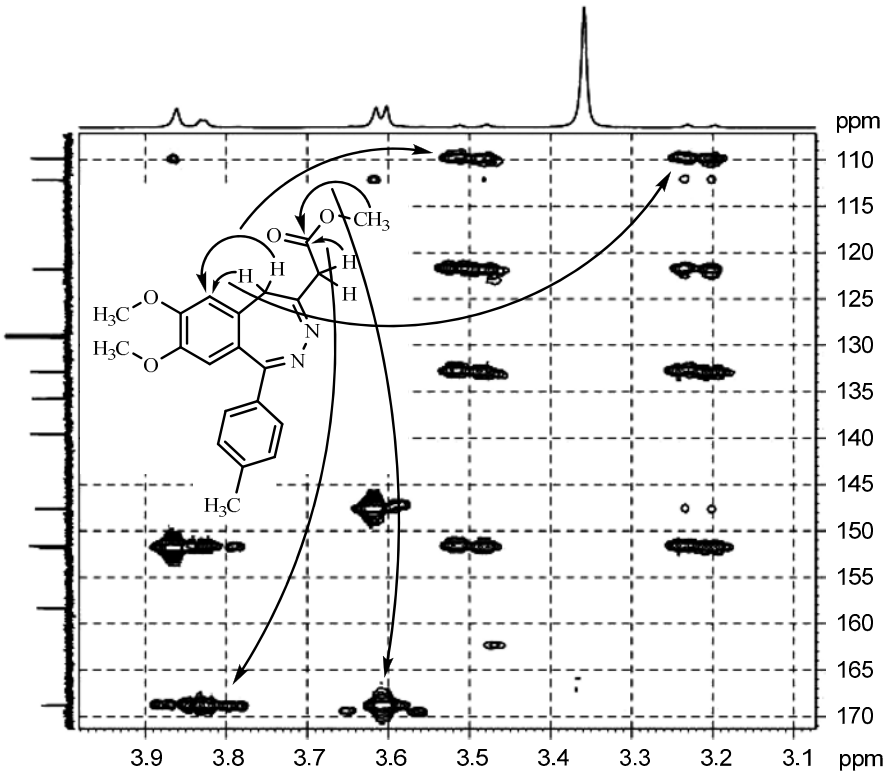



Fig. 2. Assignment of exocyclic and endocyclic methylene groups in the spectrum of compound **8c** using the HMBC procedure.

The successful employment of the Eschenmoser reaction in a series of 1-aryl-2,3-benzodiazepines has therefore enabled significant expansion of the synthetic potential of this class of heterocyclic compounds.

## EXPERIMENTAL

The IR spectra were recorded on an IR-75 instrument in KBr pellets. The $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Bruker Avance II instrument (400 and 100 MHz, respectively) in DMSO-$d_6$, internal standard was TMS. Elemental analysis was carried out on an Elementar Vario EL Cube Elemental Analyzer (C,H,N,S).

TABLE 1. Physicochemical Characteristics of the Obtained Compounds

| Compound | Empirical formula | Found, % / Calculated, % | | | Mp, °C | Yield, % |
|---|---|---|---|---|---|---|
| | | C | H | N | | |
| **7a** | $C_{20}H_{20}N_2O_4S$ | 62.37 / 62.48 | 5.13 / 5.24 | 7.41 / 7.29 | 151-152 | 70 |
| **7b** | $C_{22}H_{24}N_2O_4S$ | 63.95 / 64.06 | 5.75 / 5.86 | 6.91 / 6.79 | 107-108 | 75 |
| **7c** | $C_{21}H_{22}N_2O_4S$ | 63.19 / 63.30 | 5.44 / 5.56 | 7.16 / 7.03 | 131-132 | 65 |
| **8a** | $C_{20}H_{20}N_2O_4$ | 68.26 / 68.17 | 5.62 / 5.72 | 8.04 / 7.95 | 171-172 | 66 |
| **8b** | $C_{22}H_{24}N_2O_4$ | 69.56 / 69.46 | 6.26 / 6.36 | 7.51 / 7.36 | 129-130 | 51 |
| **8c** | $C_{21}H_{22}N_2O_4$ | 68.95 / 68.84 | 5.97 / 6.05 | 7.76 / 7.65 | 152-153 | 56 |

Melting points were determined on a Boetius hot stage apparatus and are not corrected. 1-Aryl-7,8-dimethoxy-3,5-dihydro-2,3-benzodiazepine-4-thiones **6a**,**b** were obtained by the described procedure [13].

**Synthesis of Esters 7a-c (General Method)**. A solution of NaOH (0.6 g, 0.015 mol) in $H_2O$ (5 ml) was added to a solution of thione **6a**,**b** (0.010 mol) in MeOH (50 ml) and stirred until dissolution. Chloroacetic acid methyl ester (0.120 mol) or 2-bromopropionic acid methyl ester (0.120 mol) was added to the obtained solution, and the mixture was refluxed for 30 min. The solution was cooled, diluted with water (two volumes), the solid was filtered off, dried, and recrystallized from 2-PrOH.

**Methyl (7,8-Dimethoxy-1-phenyl-5*H*-2,3-benzodiazepin-4-ylsulfanyl)acetate (7a)**. IR spectrum, ν, $cm^{-1}$: 1200 (C–C), 1620 (C=N), 1740 (O=C–O). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 3.22 (1H, d, *J* = 12.0) and 3.40 (1H, d, *J* = 12.0, 5-$CH_2$); 3.68 (3H, s) and 3.69 (3H, s, $OCH_3$, $COOCH_3$); 3.71 (1H, d, *J* = 14.4) and 3.80 (1H, d, *J* = 14.4, $SCH_2$); 3.91 (3H, s, $OCH_3$); 6.67 (1H, s, H-6); 6.91 (1H, s, H-9); 7.36-7.46 (3H, m, H Ph); 7.61 (2H, d, *J* = 7.4, H Ph). $^{13}$C NMR spectrum, δ, ppm: 31.9; 38.0; 51.8; 55.2; 55.3; 109.4; 112.0; 121.6; 127.6; 129.0; 129.2; 132.3; 138.4; 147.7; 150.3; 151.9; 157.8; 167.8.

**Methyl 2-[7,8-Dimethoxy-1-(4-methylphenyl)-5*H*-2,3-benzodiazepin-4-ylsulphanyl]propionate (7b)**. IR spectrum**,** ν, $cm^{-1}$: 1190 (C–C), 1600 (C=N), 1740 (O=C–O). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 1.31 (1.5H, d, *J* = 8.0) and 1.50 (1.5H, d, *J* = 8.0, CHC$\underline{H}_3$); 2.36 (3H, s, ArC$\underline{H}_3$); 3.21 (1H, d, *J* = 8.0) and 3.45 (1H, d, *J* = 8.0, 5-$CH_2$); 3.49 (1.5H, s) and 3.66 (1.5H, s, $COOCH_3$); 3.62 (3H, s, $OCH_3$); 3.86 (3H, s, $OCH_3$); 4.23 (0.5H, q, *J* = 8.0) and 4.29 (0.5H, q, *J* = 8.0, C$\underline{H}$Me); 6.70 (1H, s, H-6); 7.06 (0.5H, s) and 7.07 (0.5H, s, H-9); 7.26 (2H, d, *J* = 7.6, H Ar); 7.48 (2H, d, *J* = 7.6, H Ar). $^{13}$C NMR spectrum , δ, ppm: 17.5; 20.9; 38.0; 38.1; 41.1 (2C); 52.3; 52.5; 55.6; 55.8; 109.8; 109.9; 112.1; 121.8 (2C); 128.9; 129.1; 132.7; 135.7; 139.6; 147.6; 150.9; 151.2; 151.9; 158.3; 171.6; 171.9.

**Methyl [7,8-Dimethoxy-1-(4-methylphenyl)-5*H*-2,3-benzodiazepin-4-ylsulfanyl]acetate (7c)**. IR spectrum, ν, $cm^{-1}$: 1200 (C–C), 1620 (C=N), 1740 (O=C–O). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 2.39 (3H, s, ArC$\underline{H}_3$); 3.22 (1H, d, *J* = 12.8) and 3.50 (1H, d, *J* = 12.8, 5-$CH_2$); 3.63 (3H, s) and 3.64 (3H, s, $OCH_3$, $COOCH_3$); 3.74-3.78 (2H, m, $SCH_2$); 3.88 (3H, s, $OCH_3$); 6.69 (1H, s, H-6); 7.08 (1H, s, H-9); 7.26 (2H, d, *J* = 8.1, H Ar); 7.48 (2H, d, *J* = 8.1, H Ar). $^{13}$C NMR spectrum, δ, ppm: 20.9; 32.1; 37.9; 52.3; 55.6; 55.8; 109.9; 112.2; 121.8; 128.9; 129.1; 132.8; 135.8; 139.5; 147.6; 151.6; 151.8; 158.3; 168.8.

**Synthesis of Esters 8a-c (General Method)**. A mixture of compound **7a-c** (2.6 mmol) and triethyl phosphite (3 ml) was heated under reflux in a flask at 150°C for 6 h. The reaction mixture was evaporated in the vacuum of a water-jet pump to minimum volume, cooled, and *t*-BuOMe (10 ml) was added. After 12 h, the solid was filtered off, washed with *t*-BuOMe, and dried.

**Methyl (7,8-Dimethoxy-1-phenyl-5*H*-2,3-benzodiazepin-4-yl)acetate (8a)**. IR spectrum, ν, $cm^{-1}$: 1620 (C=N), 1740 (O=C–O). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 3.24 (1H, d, *J* = 13.4) and 3.51 (1H, d, *J* = 13.4, 5-$CH_2$); 3.60 (3H, s) and 3.61 (3H, s, $OCH_3$, $COOCH_3$); 3.83 (2H, br. s, $CH_2CO$); 3.87 (3H, s, $OCH_3$); 6.68 (1H, s, H-6); 7.10 (1H, s, H-9); 7.42-7.52 (3H, m, H Ph); 7.58 (2H, d, *J* = 7.2, H Ph). $^{13}$C NMR spectrum, δ, ppm: 32.9; 38.8; 53.1; 56.5; 56.6; 110.7; 113.0; 122.6; 129.1; 130.0; 130.7; 133.8; 139.3; 148.5; 152.6; 152.7; 159.3; 169.4.

**Methyl 2-[(7,8-Dimethoxy)-1-(4-methylphenyl)-5*H*-2,3-benzodiazepin-4-yl]propionate (8b)**. IR spectrum, ν, $cm^{-1}$: 1630 (C=N), 1740 (O=C–O), 2800 (CH). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 1.42 (1.5H, d, *J* = 7.2) and 1.62 (1.5H, d, *J* = 7.2, CHC$\underline{H}_3$); 2.37 (3H, s, ArC$\underline{H}_3$); 2.80 (1H, d, *J* = 12.7), 3.57 (0.5H, d, *J* = 12.7) and 3.62 (0.5H, d, *J* = 12.7, 5-$CH_2$); 3.59 (3H, s) and 3.62 (3H, s, $OCH_3$, $COOCH_3$); 3.60 (0.5H, q, *J* = 7.1) and 3.66 (0.5H, q, *J* = 7.1, C$\underline{H}$Me); 3.85 (3H, s, $OCH_3$); 6.71 (1H, s, H-6); 7.03 (0.5H, s) and 7.09 (0.5H, s, H-9); 7.26 (2H, d, *J* = 8.0, H Ar); 7.47 (1H, d, *J* = 8.0) and 7.50 (1H, d, *J* = 8.0, H Ar). $^{13}$C NMR spectrum, δ, ppm: 14.3; 14.8; 20.9; 34.6; 35.4; 45.7; 46.5; 51.9; 55.5; 55.6; 55.7; 55.8; 109.7; 109.9; 112.0; 121.5 (2C); 128.9; 129.1; 133.3; 133.7; 135.8 (2C); 139.5; 147.4 (2C); 151.6; 155.0; 155.4; 157.1; 157.2; 172.0; 172.1.

**Methyl [(7,8-Dimethoxy)-1-(4-methylphenyl)-5*H*-2,3-benzodiazepin-4-yl]acetate (8c)**. IR spectrum, ν, $cm^{-1}$: 1620 (C=N), 1740 (O=C–O), 2900, 2950 ($CH_2$). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 2.36 (3H, s, ArC$\underline{H}_3$); 3.22 (1H, d, *J* = 12.0) and 3.49 (1H, d, *J* = 12.0, 5-$CH_2$); 3.60 (3H, s) and 3.62 (3H, s, $OCH_3$,

$COOCH_3$); 3.81-3.85 (2H, m, $CH_2CO$); 3.86 (3H, s, $OCH_3$); 6.68 (1H, s, H-6); 7.09 (1H, s, H-9); 7.26 (2H, d, $J$ = 8.0, H Ar); 7.48 (2H, d, $J$ = 8.0, H Ar). $^{13}C$ NMR spectrum, δ, ppm: 20.9; 32.1; 37.9; 52.3; 55.6; 55.8; 109.9; 112.2; 121.8; 128.9; 129.1; 132.8; 135.7; 139.5; 147.6; 151.6; 151.8; 158.3; 168.8.

## REFERENCES


1. E. Horvath, K. Horvath, T. Hamori, M. Feketeb, S. Solyom, and M. Palkovitsc, *Progr. Neurobiol.*, **60**, 309 (2000).
2. D. P. Munro and J. T. Sharp, *Tetrahedron. Lett.*, **23**, 345 (1982).
3. O. I. Kharaneko, V. Yu. Popov, and S. L. Bogza, *Khim. Geterotsikl. Soedin.*, 343 (2013). [*Chem. Heterocycl. Compd.*, **49**, 317 (2013).]
4. K. M. Khabarov, O. I. Kharaneko, and S. L. Bogza, *Khim. Geterotsikl. Soedin.*, 594 (2009). [*Chem. Heterocycl. Compd.,* **45**, 468 (2009).]
5. R. Gitto, V. Orlando. S. Quartarone, G. De Sarro, A. De Sarro, E. Russo, G. Ferreri, and A. Chimirri, *J. Med. Chem.*, 46, 3758 (2003).
6. E. B. Knott, *J. Chem. Soc.*, 916 (1955).
7. A. Fischli and A. Eschenmoser, *Angew. Chem*., *Int. Ed. Engl*., **6**, 866 (1967).
8. P. Loeliger and E. Fluckiger, *Org. Synth.*, **55**, 127 (1976).
9. S. Singh, J. M. Köhler, A. Schober, and G. A. Gross, *Beilstein J. Org. Chem.*, **7**, 1164 (2011).
10. Y. Inubushi and T. Ibuka, *Heterocycles*, **8**, 633 (1977).
11. B. A. D. Neto, A. A. M. Lapis, A. B. Bernd, and D. Russowsky, *Tetrahedron*, **65**, 2484 (2009).
12. S. L. Bogza, I. K. Kobrakov, V. Yu. Popov, E. S. Sizonenko, and S. Yu. Suikov, *Visnik Kharkiv. Natsional Univ*., No. 1026, *Khimiya*, Issue 21 (44), 122 (2012).
13. A. Chimirri, G. De Sarro, A. De Sarro, R. Gitto, S. Quartarone, M. Zappala, A. Constanti, and V. Libri, *J. Med. Chem.*, **41**, 3409 (1998).