SYNTHESIS, SPATIAL STRUCTURE AND ANALGESIC ACTIVITY OF ETHYL 4-HYDROXY-1-PHENYL-2,2-DIOXO-1*H*-2λ⁶,1-BENZOTHIAZINE-3-CARBOXYLATE

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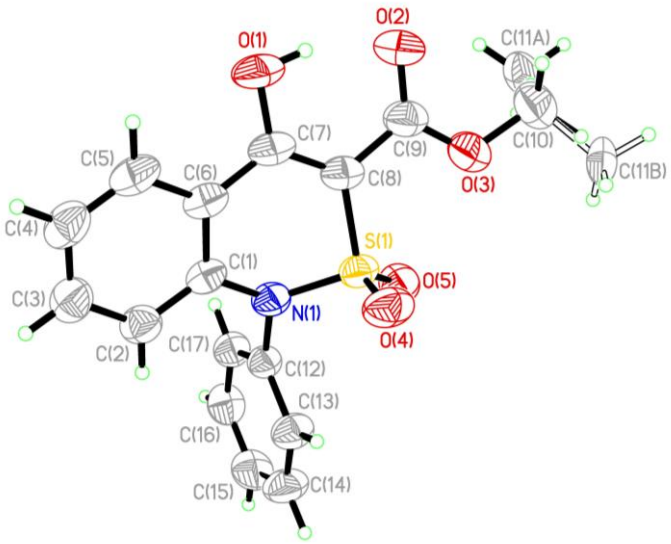
Alkyl 4-R-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxylates hold interest not only as highly effective analgesics but also as a basis for synthesis of various amidated derivatives with wide specter of biological properties. While working out the preparatory method of obtaining such compounds accessible alkyl 2-[2-(R-carbonyl)phenylsulfamoyl]-acetates were noticed to demand powerful enough bases like sodium alcoholates to be used for their successful enclosure into corresponding 2,1-benzothiazines and, moreover, to show tendency to re-esterification, which is to be taken into account while choosing condensing agent and solvent for synthesis. In some cases such as heterocyclization in sodium hydride/tetrahydrofuran, sodium hydride/DMF or potassium *tert*-butylate/DMSO systems no special warnings as to possibility of side processes are needed. However, the situation is quite different in case of more accessible, safe and comfortable to use condensing agents based on lower alcohols with normal structure. To obtain sodium alcoholate it is advisable to use as a solvent and a reagent one and the same alcohol as that whose remains are present in the initial alkyl 2-[2-(R-carbonyl)phenylsulfamoyl]-acetates. Otherwise a mixture of alkyl esters of some or other 4-R-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxylic acid will be obtained as a result, which is not always acceptable.

During our further research it was ascertained that not only interim alkyl 2-[2-(alkoxycarbonyl)phenylsulfamoyl]-acetates but also final alkyl 4-hydroxy-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxylates derived from them are prone to alkoxy group interchange. What more, in case of the former ones re-esterification takes place in abundance of spirit with powerful bases present whereas in case of the latter ones the possibility of this conversion became unexpectedly easy under usual crystallization from alcohol without any catalyst added. So, for instance, methyl 4-hydroxy-1-phenyl-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxylate converts up to about 30% into its ethyl analogue already after a short-time (3 to 5 minutes) heating in ethanol. After the time of processing with boiling ethanol is increased up to 1 hour the conversion of methyl ether into ethyl is complete.

The peculiarities of the spatial structure of the compound obtained have been studied. In particular, it has been determined with the help of ^{1}H-NMR spectroscopy and X-ray diffraction analysis that in solution the 1-*N*-phenyl substituent is located at an angle of about 60° to the plane formed by the aminophenylcarbinol fragment of 2,1-benzothiazine, whereas in the crystal this angle increases to 80° due to the effects of packing:



The analgesic activity of the synthesized methyl 4-hydroxy-1-phenyl-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxylate and its ethyl analogue was studied on the standard model of the thermal tail-flick procedure in white male rats weighing 180–200 g (Tail Immersion Test).

Initial methyl 4-hydroxy-1-phenyl-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxy-late is known to show no analgesic properties. That is why it is interesting from the point of view of further research on new pain killers to observe a possible impact of the changes in the ester part of the molecule on the pharmacological effect.

Comparative analysis of the experimental data presented in the table proves without doubt that transition from methyl ester to its analogue is accompanied by a noticeable enforcement of analgesic properties reaching Piroxicam level. It is interesting to note that in case of *N*-alkylsubstituted alkyl 4-hydroxy-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxylates analogous modification causes quite the opposite pharmacological effect.

Thus, the presented research shows that even minor structural changes in the ester fragment of alkyl 4-hydroxy-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxylates can have a considerable impact on their biological properties. Consequently, as well as various amidated derivatives of 1-R-4-hydroxy-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxylic acids it would be advisable to include their esters into the search for new prospective analgesics. The more so because the chemical modification of this fragment of the molecule is not difficult to be obtained practically and may principally be rather diverse.