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Syntheses of Compounds Active toward Glutamate Receptors: I. New Preparative Synthesis of Aminoindandicarboxylic Acid (AIDA)*

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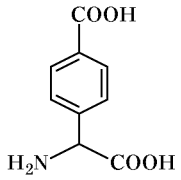
Abstract—A preparative procedure has been developed for the synhtesis of 1-aminoindan-1,5-dicarboxylic acid which is a new group I metabotropic glutamate receptor antagonist.

In the last decade, the number of publications concerning structural design and synthesis of compounds selective for metabotropic glutamate receptors (mGluR) considerably increased. Metabotropic glutamate receptors are proteins partially "immersed" into a cell membrane and having (*S*)-glutamic acid binding sites. Activation of mGluR by glutamic acid launches intracellular metabolic processes with participation of several membrane proteins, which successively react with each other. In the recent time it was shown that disorder of the cellular mechanism for regulation of the mGluR activation may be among factors responsible for pathogenesis of various neurodegenerative diseases, such as Alzheimer's disease, Huntington's chorea, etc. Just realization of this fact gave an impetus to dramatically increased interest in chemical compounds capable of acting as mGluR ligands [1–3].

The family of metabotropic glutamate receptors includes at least 8 different subtypes which can be divided into 3 groups with respect to their amino acid sequence, signal transduction mechanism, and sensitivity to some substances. Metabotropic glutamate receptors of each subtype can be a biological target in the therapic treatment of the above diseases. Here, potential neuroprotective activity should be intrinsic to compounds which are antagonists at group I metabotropic glutamate receptors or agonists at groups II and III mGluR. It is important that the main problem in the design of such structures is search for compounds highly selective for a definite subtype of metabotropic glutamate receptors [1].

Nonspecific antagonists at group I mGluR are numerous derivatives of carboxyphenylglycine (**I**) [4]. Recent study of physiological activity of carboxyphenylglycine analogs with a limited conformational mobility has shown that 1-aminoindan-1,5-dicarboxylic acid (**II**, AIDA) is not very active but (at low concentrations) highly selective antagonist at $mGluR_1$ subtype receptors which belong to group I metabotropic glutamate receptors [5]. Due to its high selectivity, dicarboxylic acid **II** is now widely used as a "molecular tool" for studying the corresponding receptor subtype. In addition, extensive studies are carried out on the synthesis of its analogs as potential neuroprotecting agents.



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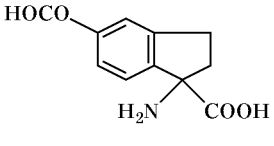

II

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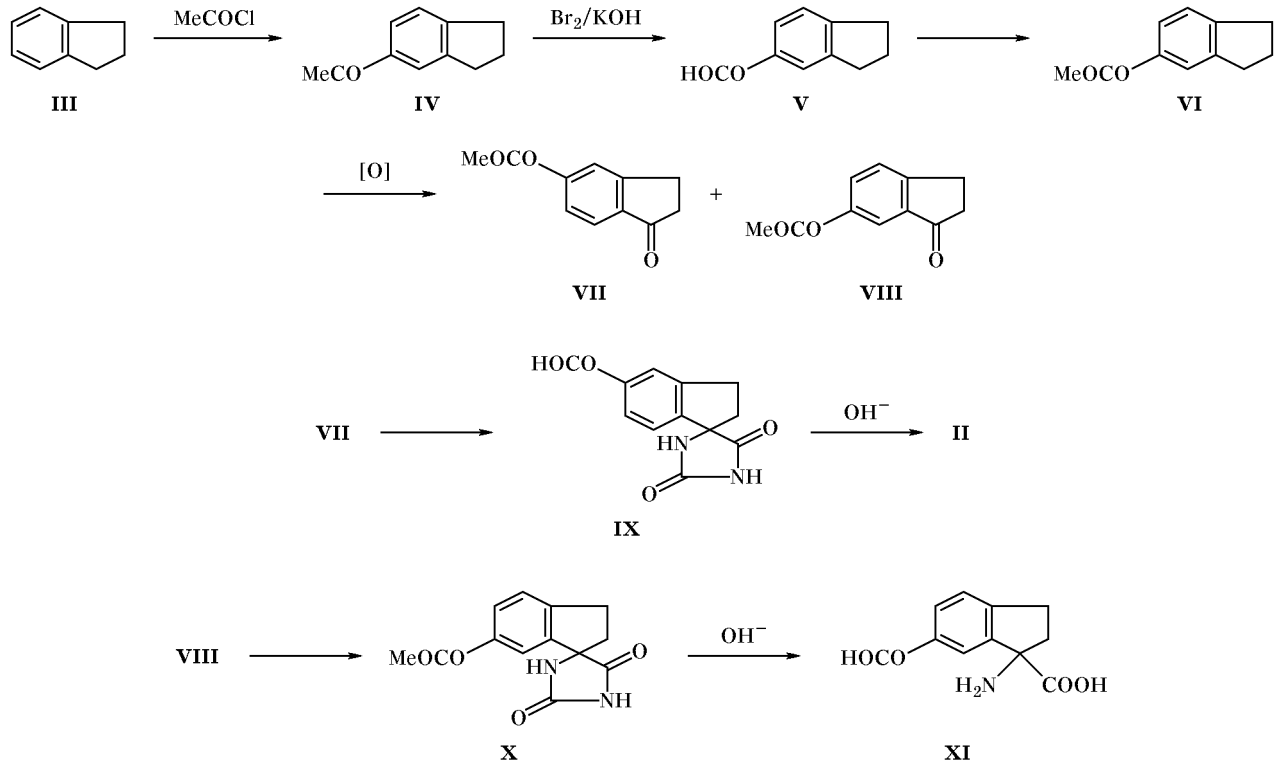
Scheme 1.



The present communication opens a series of our reports on the synthetic program aimed at developing new methods for preparation of compound **II** and its analogs and studying their pharmacological properties. The known procedure for preparation of amino acid **II** [5] allowed us to obtain only small amounts of the target compound. Therefore, the goal of this study was to develop a new preparative procedure for the synthesis of 1-aminoindan-1,5-dicarboxylic acid (**II**) and isomeric 1-aminoindan-1,6-dicarboxylic acid (**XI**) (Scheme 1). As starting compound we used indan (**III**). Its acylation with acetyl chloride (4 h) gave 5-acetylindan (**IV**) in quantitative yield. Ketone **IV** was brought into haloform reaction to obtain 5-indancarboxylic acid (**V**). The optimal conditions at that stage (yield of **V** 99%) were heating of the reaction mixture for 5 h at 55°C.

Methyl 5-indancarboxylate (**VI**) was prepared by a standard procedure, from the corresponding acyl chloride and sodium methoxide. The subsequent oxidation of ester **VI** with chromium(VI) oxide led to formation of two isomeric products, methyl 1-oxoindan-5- and -6-carboxylates **VII** and **VIII**, which were separated by recrystallization from ethyl acetate–petroleum ether, followed by column chromatography on silica gel. As a result, we isolated isomeric esters **VII** and **VIII** in 20 and 25% yield, respectively. The structure of compounds **VII** and **VIII** was proved by the data of ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum of methyl 1-oxoindan-5-carboxylate (**VII**) contained a doublet at δ 7.76 ppm (1H, 7-H, H_{arom}), a doublet at δ 8.00 ppm (1H, 6-H, H_{arom}), and a singlet at δ 8.12 ppm (1H, 4-H, H_{arom}). In the ^{1}H NMR spectrum of 6-methoxycarbonyl analog **VIII**, the doublet signal corresponding to 4-H appeared at δ 7.56 ppm, the doublet from 5-H was observed at δ 8.24 ppm, and the singlet from 7-H was located at δ 8.36 ppm. We thus unambiguously identified isomers **VII** and **VIII**. The purity of each isomer was checked by GLC.

Ketones **VII** and **VIII** were converted into the corresponding hydantoins. A known [5, 6] procedure for the synthesis of hydantoins from ketones by the action of sodium cyanide and ammonium carbonate requires severe conditions (increased pressure). We have found that this procedure cannot be applied to the synthesis of ketone **VII**, for the reaction is accompanied by strong tarring and the yield of the target product is very poor. We have proposed a procedure for preparation of hydantoins under milder conditions (under atmospheric pressure), which has not been applied previously for indan systems. The reactions

were carried out in aqueous DMF at 90–100°C (reaction time 36 h). As a result, we isolated 2′,4′-dioxoindan-1-spiro-5′-imidazolidine-5-carboxylic acid (**IX**) and methyl 2′,4′-dioxoindan-1-spiro-5′-imidazolidine-6-carboxylate (**X**) in 65 and 75% yield, respectively. The ^{1}H NMR spectra of hydantoins **IX** and **X** contained characteristic signals from the amide protons in the δ regions 8.03–8.55 and 9.02–10.9 ppm. In the IR spectra of **IX** and **X** we observed absorption bands from the amide carbonyl groups at 1600–1620 cm^{-1}.

By hydrolysis of compounds **IX** and **X** we obtained the corresponding α-amino acids **II** and **XI**. The general procedure for hydrolysis under pressure [7] turned out to be inapplicable for the preparation of amino acids of the indan series. Also, there were difficulties in the isolation of the amino acids from the reaction mixtures. We have studied the hydrolysis of **IX** and **X** in various solvents (H_2O, ethanol, DMF) using such bases as NaOH and $Ba(OH)_2$ with variation of the other parameters. The best results were obtained in water with $Ba(OH)_2$ as a base at a reactant ratio (hydantoin–base–ammonium carbonate) of 1:1:2.5 at 100°C (reaction time 12.5 h). These conditions ensured synthesis of amino acids **II** and **XI** in 70% yield. The structure of the products was confirmed by the ^{1}H and ^{13}C NMR spectra. Amino acid **II** shows in the ^{1}H NMR spectrum a singlet at δ 5.5 ppm, which belongs to the NH_2 protons, while those assignable to amide NH protons are absent. A characteristic signal in the ^{13}C NMR spectrum is that from the quaternary C^1 carbon atom, which is displaced to δ_C 88 ppm.

Thus we have developed a preparative procedure for the synthesis of aminoindandicarboxylic acids. Our preliminary results on docking of several AIDA analogs (in particular, of those containing various substituents instead of the terminal carboxy group) into a computer-simulated $mGluR_1$ model (which was built up on the basis of the X-ray diffraction data [8]) showed the possibiliy for some compounds to exhibit a higher activity and/or selectivity for $mGluR_1$, as compared to AIDA. The proposed procedure opens the way to substituted α-amino acids of the indan series, which could considerably increase the number of available AIDA analogs.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-400 spectrometer (400 MHz for ^{1}H) in $CDCl_3$ and DMSO-d_6 using tetramethylsilane as internal reference. The IR spectra were obtained on a UR-20 instrument from solutions in carbon tetrachloride. GLC analysis was performed on a Chrom-5M gas chromatograph equipped with a flame-ionization detector and a BP-1 25-m × 0.25-mm capillary column (carrier gas helium, flow rate of 1.5 ml/min). The progress of reactions was monitored by thin-layer chromatography on Silufol plates. Merck 60 silica gel (70–230 mesh ASTM) was used for column chromatography.

1-Aminoindan-1,5-dicarboxylic acid (II). A mixture of 0.31 g (0.0012 mol) of compound **IX** and 0.38 g (0.0012 mol) of $Ba(OH)_2 \cdot 8H_2O$ in 10 ml of water was heated for 10 h under reflux. It was then cooled to room temperature, 0.58 g (0.006 mol) of ammonium carbonate was added, and the mixture was refluxed for 2.5 h. The precipitate was filtered off, the filtrate was evaporated, and the residue was subjected to cation-exchange chromatography on Dowex 50 × 200 using a 10% solution of pyridine in water as eluent. Yield 0.2 g (71%), yellowish crystals, mp >300°C (cf. [5]). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.42 m (1H, CH_2), 2.65 m (1H, CH_2), 3.18 t (2H, CH_2), 7.52 d (1H, H_{arom}), 7.88 d (1H, H_{arom}), 7.98 s (1H, H_{arom}).

5-Acetylindan (IV). Aluminum chloride, 21.8 g (0.16 mol), was added in portions to a solution of 19.3 g (0.16 mol) of indan and 16.1 g (0.20 mol) of acetyl chloride in 100 ml of benzene, which was stirred at 0°C under argon. The mixture was allowed to warm up to room temperature, stirred for 4 h, and poured into 30 ml of water containing ice. It was acidified with 10% hydrochloric acid and extracted with ethyl acetate (3 × 20 ml). The combined extracts were washed with 50 ml of a saturated solution of sodium chloride, dried over calcined sodium sulfate, and evaporated. Yield of **IV** 25 g (98%), yellow oily substance. IR spectrum: ν(C=O) 1680 cm^{-1}. The product had a purity of 100% (according to GLC).

5-Indancarboxylic acid (V). Bromine, 48.9 g (0.3 mol), was quickly added to a solution of 56 g (1 mol) of KOH in 200 ml of water while stirring at 0°C. 5-Acetylindane (**IV**), 12.3 g (0.076 mol), was slowly added to the resulting solution, the mixture was heated for 3 h at 55°C, 11.4 g (0.06 mol) of $Na_2S_2O_5$ was added, and the mixture was acidified to pH 3 with concentrated hydrochloric acid. The precipitate was filtered off and dried in air. Yield 11.8 g (95%), colorless crystals, mp 165°C; published data [5]: mp 165–166°C. ^{1}H NMR spectrum, δ, ppm: 2.5 m and 3.3 m (CH_2), 7.8 d (1H, 7-H), 8.4 d (1H, 4-H), 8.0 s (1-H, 6-H).

Methyl 5-indancarboxylate (VI). Thionyl chloride, 6 ml, was added on cooling to a solution of 10 g (0.06 mol) of 5-indancarboxylic acid (**V**) in 10 ml of dry benzene. The mixture was heated for 2 h under reflux until gaseous products no longer evolved and was then heated for 1 h under reduced pressure to remove excess thionyl chloride. 5-Indancarbonyl chloride thus obtained, 11.14 g (0.06 mol), was added dropwise at 0°C under argon to a solution of 3.24 g (0.065 mol) of sodium methoxide in 20 ml of anhydrous methanol. The mixture was stirred for 3 h, poured ino ice water, and extracted with diethyl ether (3 × 50 ml). The combined extracts were dried over calcined sodium sulfate and evaporated, and the remaining dark brown oily material was subjected to flash chromatography on silica gel using petroleum ether as eluent. Yield 9.64 g (90%), yellow oily substance (purity 99%, GLC).

Oxidation of methyl 5-indancarboxylate. A solution of 7 g (0.07 mol) of CrO_3 in a mixture of 27 ml of acetic acid and 11.6 ml of water was added over a period of 30 min to a solution of 5 g (0.028 mol) of methyl 5-indancarboxylate in 13.5 ml of glacial acetic acid, which was stirred at room temperature. The mixture was stirred for 12 h, diluted with 60 ml of water, and extracted with ethyl acetate (4 × 50 ml). The combined extracts were washed with a 10% solution of Na_2CO_3 (3 × 30 ml) and a concentrated solution of sodium chloride (30 ml), dried over calcined sodium sulfate, and evaporated under reduced pressure. The residue, a dark yellow oily substance, was recrystallized from ethyl acetate–petroleum ether and was then purified by flash chromatography on silica gel using petroleum ether–ethyl acetate (85 : 15) as eluent. We isolated 1.15 g (20%) of methyl 1-oxoindan-5-carboxylate (**VII**) and 1.44 g (25%) of methyl 1-oxoindan-6-carboxylate (**VIII**) as colorless crystalline substances with mp 111°C (for both isomers); published data [5]: mp 111–112°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: compound **VII**: 2.76 t (2H, CH_2), 3.20 t (2H, CH_2), 3.95 s (3H, CH_3), 7.56 d (1H, H_{arom}), 8.24 d (1H, H_{arom}), 8.36 s (1H, H_{arom}); **VIII**: 2.76 t (2H, CH_2), 3.20 t (2H, CH_2), 3.95 s (3H, CH_3), 7.76 d (1H, H_{arom}, 8.12 s (1H, H_{arom}).

2′,4′-Dioxoindan-1-spiro-5′-imidazolidine-5-carboxylic acid (IX). A solution of 0.13 g (0.0026 mol) of sodium cyanide in 2 ml of water was added to a solution of 0.73 g (0.0076 mol) of ammonium carbonate and 0.32 g (0.0017 mol) of methyl 1-oxoindan-5-carboxylate in 3 ml of DMF. The mixture was heated for 36 h at 90°C and cooled, 50 ml of ethyl acetate was added, and the mixture was washed with 60 ml of water. The product was extracted into 30% aqueous NaOH (60 ml). The aqueous phase was separated and acidified to pH 5 with hydrochloric acid. Acid **IX** was extracted into ether (3 × 50 ml), the combined extracts were dried over calcined sodium sulfate and evaporated, and the residue was recrystallized from benzene. Yield 0.28 g (65%), light brown crystals, mp 252°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.43 m (1H, CH_2), 2.54 m (1H, CH_2), 3.10 d (2H, CH_2), 7.69 d (1H, H_{arom}), 7.87 d (1H, H_{arom}), 7.94 s (1H, H_{arom}), 8.10 s (1H, NH), 8.43 s (1H, NH).

Methyl 2′,4′-dioxoindan-1-spiro-5′-imidazolidine-6-carboxylate (X). A solution of 0.83 g (0.01 mol) in 3 ml of water was added to a solution of 4.5 g (0.047 mol) of ammonium carbonate and 2 g (0.01 mol) of methyl 1-oxoindan-6-carboxylate in 20 ml of DMF. The mixture was heated for 36 h at 90°C and cooled, 100 ml of ethyl acetate was added, and the mixture was washed with 100 ml of water and extracted with 100 ml of a 30% solution of sodium hydroxide. The aqueous phase was separated and acidified to pH 5 with hydrochloric acid. Ester **X** was extracted into ether (3 × 50 ml), the combined extracts were dried over calcined sodium sulfate and evaporated, and the residue was recrystallized from benzene. Yield 2 g (75%), light brown crystals, mp 250°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.20 m (1H, CH_2), 2.48 m (1H, CH_2), 3.05 m (2H, CH_2), 3.85 s (CH_3), 7.42 d (1H, H_{arom}), 7.62 s (1H, H_{arom}), 7.95 d (1H, H_{arom}), 8.55 s (1H, NH), 10.90 s (1H, NH).

1-Aminoindan-1,6-dicarboxylic acid (XI). A mixture of 0.5 g (0.0019 mol) of compound **X** and 0.61 g (0.0019 mol) of $Ba(OH)_2 \cdot 8H_2O$ in 10 ml of water was heated for 10 h under reflux. The mixture was cooled to room temperature, 0.46 g (0.005 mol) of ammonium carbonate was added, and the mixture was refluxed for 2.5 h. The precipitate was filtered off, and the filtrate was evaporated. The residue was purified by cation-exchange chromatography on Dowex 50 × 200 using a 10% solution of pyridine in water as eluent. Yield 0.3 g (72%), yellowish crystals, mp >300°C (cf. [5]). ^{1}H NMR spectrum (D_2O), δ, ppm: 2.22 m (1H, CH_2), 2.55 m (1H, CH_2), 2.96 t (2H, CH_2), 7.22 d (1H, H_{arom}), 7.56 s (1H, H_{arom}), 7.76 d (1H, H_{arom}).

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