Russian Journal of Organic Chemistry, Vol. 38, No. 12, 2002, pp. 1769–1774. Translated from Zhurnal Organicheskoi Khimii, Vol. 38, No. 12, 2002, pp. 1830–1835.

Syntheses of Compounds Active toward Glutamate Receptors: II.* Synthesis of Spiro Hydantoins of the Indan Series**

E. D. Matveeva[1], T. A. Podrugina[1], N. Yu. Morozkina[1], O. N. Zefirova[1], I. V. Seregin[1], S. O. Bachurin[2], R. Pellicciari[3], and N. S. Zefirov[1]

[1] *Faculty of Chemistry, Moscow State University, Vorob'evy gory, Moscow, 119899 Russia e-mail: edmatveeva@mail.ru*

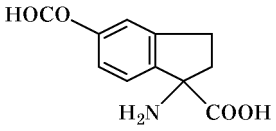
[2] *Institute of Physiologically Active Substances, Russian Academy of Sciences, Chernogolovka, Moscow oblast, 142432 Russia*

[3] *Universita degli studi di Perugia, via del Liceo, 1-06123 Perugia, Italy*

Received February 20, 2002

Abstract—The article describes a general procedure for synthesizing hydantoins of the indan series, which makes it possible to obtain bioisosteric analogs of 1-aminoindan-1,5-dicarboxylic acid, a group I metabotropic glutamate receptor antagonist.

It is well known that interest in hydantoins arises mainly from the possibility for their further use in the synthesis of biologically active amino acids. For example, the ability of hydantoins to undergo hydrolysis with formation of amino acids was utilized by us in the preparative method for synthesizing 1-aminoindan-1,5-dicarboxylic acid (**I**, AIDA) which is a selective antagonist (blockator) at group I metabotropic glutamate receptors ($mGluR_1$ subtype) [1].



I

Replacement of the aromatic carboxy group in molecule **I** by phosphono group also gives $mGluR_1$ antagonist [2]. By computer simulation we showed that some other derivatives of acid **I** (e.g., its analog containing a tetrazole moiety at C^5) can also be capable of binding to glutamate receptors of the same subtype. Taking into account the above stated, the goal of the present study was to develop a general procedure for synthesizing hydantoins of the indan series with a view to obtain various isosteric and bioisosteric analogs of 1-aminoindan-1,5-dicarboxylic acid (**I**).***

As starting compound for the synthesis of 5-substituted indan-1-spiro-5′-hydantoins we selected 5-bromoindan-1-one which was prepared in several steps from *m*-bromobenzaldehyde (**II**) (Scheme 1). In the final step, 3-(*m*-bromophenyl)propionyl chloride (**VIII**) was brought into intramolecular cyclization according to Friedel–Crafts. We have found conditions ensuring formation of 5-bromoindan-1-one (**IX**) as the only product of the cyclization of 3-(*m*-bromophenyl)propionyl chloride (**VIII**).

Spiro hydantoins of the indan series having phosphinoyl and tetrazolyl groups at the indan C^5 atom were obtained by substitution of the bromine atom in **IX**. It is known that triethyl phosphite reacts with

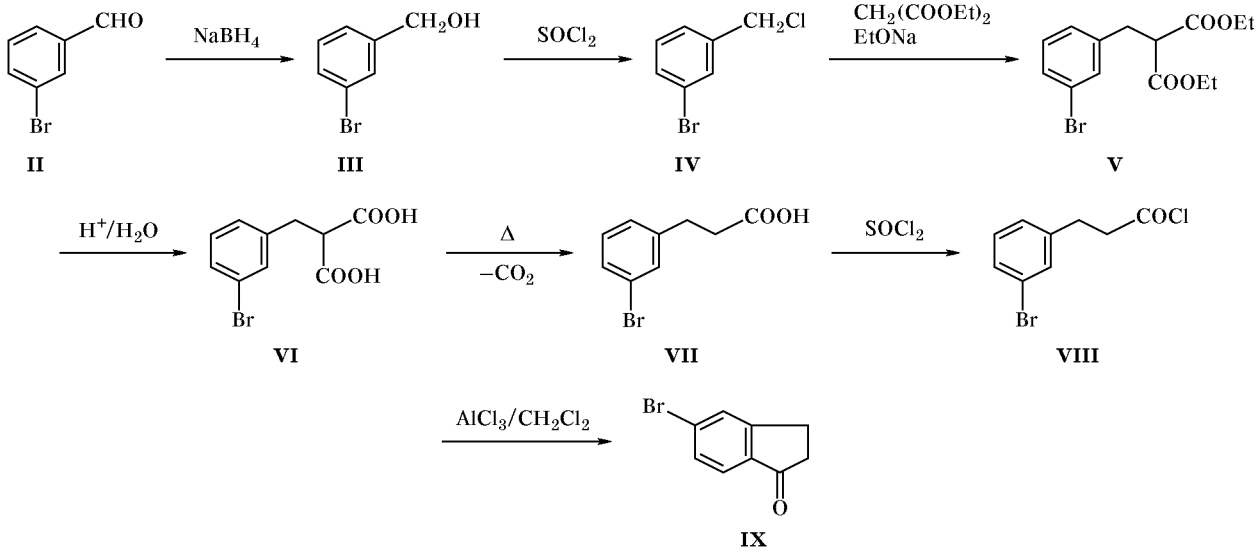
* For communication I, see [1].

** This study was financially supported by the Russian Foundation for Basic Research (project no. 01-03-33085) and by the Leading Scientific Schools Program (project no. 00-15-97454).

*** *Bioisoster* is a compound obtained by replacement of an atom or group by other related atoms or groups with retention of biological activity. Such a replacement is aimed at creating a new compound whose properties are similar to those of the parent compound.

1070-4280/02/3812-1769 $27.00 © 2002 MAIK "Nauka / Interperiodica"

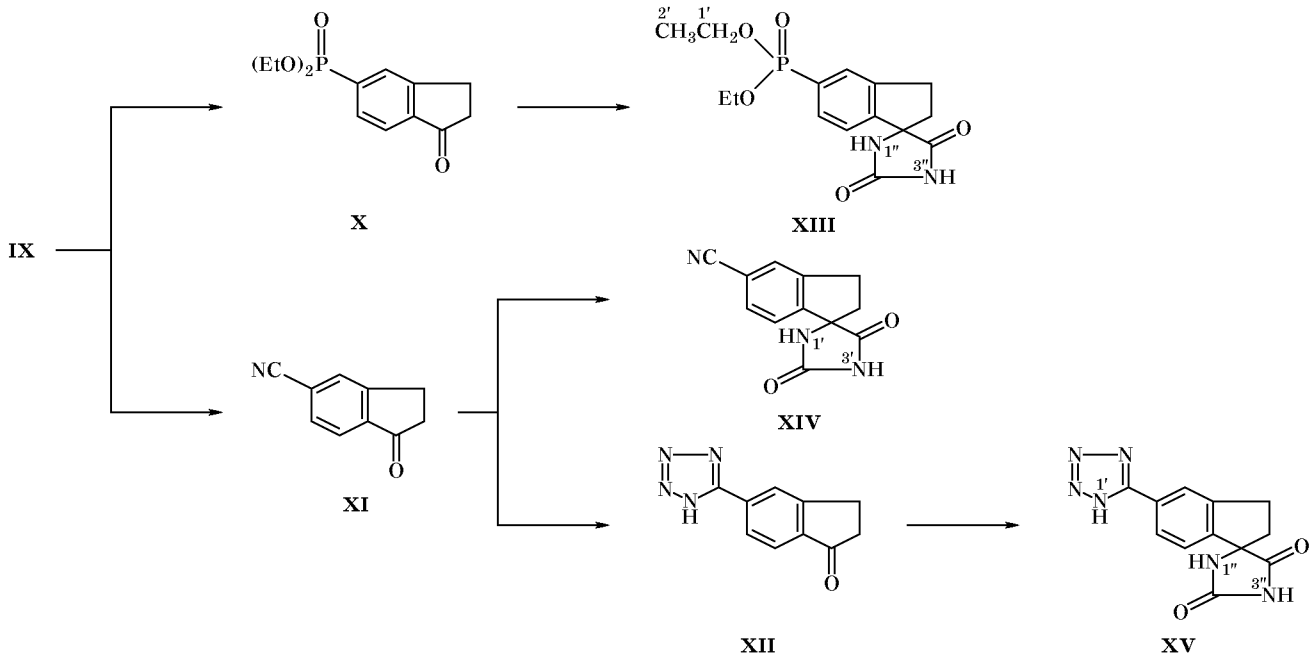
Scheme 1.



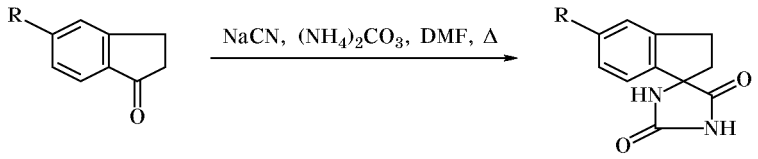
aromatic ketones under conditions of phase-transfer catalysis in the presence of palladium(II) acetate and triphenylphosphine as ligand, yielding the corresponding diethoxyphosphinoyl derivatives [3]. We have modified this procedure as applied to indan systems. By varying the reactant ratio and reaction time, we have found that the best results are obtained at an equimolar ratio of indanone to diethyl hydrogen phosphite on heating for 6 h at 90°C in the presence of 2 mol % of palladium(II) acetate. The structure of phosphonate **X** was confirmed by the ^{1}H and ^{31}P NMR spectra.

1-Oxoindan-5-carbonitrile (**XI**) was synthesized by nucleophilic substitution of the bromine atom in **IX** by cyano group. For this purpose, compound **IX** was treated with 1 equiv of copper(I) cyanide [4]. The maximal yield of **XI** was obtained on heating the reactants in boiling DMF for at least 15 h. In such a way, nitrile **XI** was isolated in 60% yield, and its structure was confirmed by the ^{1}H NMR and IR

Scheme 2.



Scheme 3.



IX, XVI **XVII, XVIII**

IX, **XVII**, R = Br; **XVI**, **XVIII**, R = H.

spectra. The ^{1}H NMR spectrum of **XI** contained two triplets at δ 2.75 and 3.16 ppm, which belong to CH_2 protons of the indan fragment, and multiplet signals at δ 7.75, 7.85, and 8.14 ppm due to aromatic protons. Signals from the aromatic protons in the cyano-substituted benzene ring are located in a weaker field than the corresponding signals of 5-bromoindanone **IX** (δ 7.27, 7.32, and 7.42 ppm). Compound **XI** showed in the IR spectrum an absorption band at 2220 cm^{-1}, which is typical of a cyano group.

5-Tetrazolyl derivatives can be synthesized by reaction of nitriles with sodium azide and ammonium chloride [5]. We tried to apply the same procedure to the synthesis of tetrazolyl-substituted indanone **XII**. The best results were obtained when cyanoindanone **XI**, sodium azide, and ammonium chloride were taken at a ratio of 1 : 1.3 : 1.3, respectively. The structure of 5-(1*H*-tetrazol-5-yl)indan-1-one (**XII**) was proved by the IR and ^{1}H NMR spectra. In the ^{1}H NMR spectrum of **XII** we observed two triplets at δ 2.84 and 3.00 ppm, which correspond to methylene protons of the indan moiety. Signals of the aromatic protons appeared as multiplets at δ 7.71 and 7.81 ppm and a singlet at δ 8.14 ppm. In addition, a singlet at δ 9.23 ppm was present, which belongs to the NH proton in the tetrazole ring. The IR spectrum of **XII** contained absorption bands due to stretching vibrations of the C=N and N=N bonds in the tetrazole ring (1375 and 1465 cm^{-1}) and a band at 1720 cm^{-1}, which is typical of carbonyl stretching vibrations.

General procedure for the synthesis of hydantoins with a spiro-fused indan moiety was developed using 1-indanone as model compound. It was brought into the Bucherer–Bergs reaction according to Scheme 3, i.e., treated with sodium cyanide and ammonium chloride (reactant ratio 1 : 1.5 : 4.5) on heating in aqueous DMF. The optimal conditions are given in table. The procedure for purification of the products was based on different solubilities of their protonated and neutral froms in water; as a result, the target compounds were isolated in 45–88% yield.

The structure of the hydantoin derivatives was confirmed by the ^{1}H NMR and IR spectra (see table). All these compounds showed in the ^{1}H NMR spectra signals from the amide NH protons at δ 8.03–8.55 (1′-H) and 9.02–10.9 ppm (3′-H), which are typical of hydantoins. The IR spectra contained amide carbonyl absorption bands at 1600–1620 cm^{-1}. In the ^{1}H NMR spectrum of compound **XV** we also observed a singlet at δ 8.35 ppm, which belongs to the NH proton in the tetrazole ring; the latter gives rise to IR bands at 1380 and 1460 cm^{-1} due to stretching vibrations of the C=N and N=N bonds. Stretching vibrations of the cyano group in hydantoin **XIV** appear in the IR spectrum at 2210 cm^{-1}.

Thus we have proposed a general procedure for preparation of hydantoins of the indan series on the basis of the Bucherer–Bergs reaction. This procedure makes it possible to obtain isosteric and bioisosteric analogs of 5-aminoindan-1,5-dicarboxylic acid. It should be noted that metabolic transformations of hydantoins give rise to amino acids [6]; therefore, these compounds also attract interest as potential physiologically active substances, namely as a certain kind of prodrugs.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-400 spectrometer (400 MHz for ^{1}H) using $CDCl_3$ and DMSO-d_6 as solvents and tetramethylsilane as internal reference. The IR spectra were measured on a UR-20 insrument from solutions in carbon tetrachloride. 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.

***m*-Bromobenzyl alcohol (III).** Sodium tetrahydridoborate, 1.14 g (0.03 mol), was added in small portions to a solution of 10.18 g (0.055 mol) of *m*-bromobenzaldehyde in 22 ml of ethanol. The mixture was stirred for 1 h on cooling with ice water, the resulting white suspension was evaporated to dryness on a rotary evaporator, and the residue was dissolved in water. The solution was extracted with diethyl ether (3 × 20 ml), the combined extracts were dried over

Conditions of synthesis, yields, and spectral parameters of compounds **XIII**–**XV**, **XVII**, and **XVIII**

Comp. no.	Reaction conditions	Yield, %	NMR and IR spectra
XIII	20 h, 90°C	66	^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.24 t (6H, CH_3), 2.75 t (2H, CH_2), 2.88 t (2H, CH_2), 4.08 m (2H, OCH_2), 7.71 d (1H, H_{arom}), 7.78 d (1H, H_{arom}), 7.97 d (1H, H_{arom}), 8.48 s (1H, 1″-H), 10.85 s (1H, 1″-H). IR spectrum: 1615 cm^{-1} (δNH)
XIV	30 h, 100°C	60	^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.48 d (1H, CH_2), 2.54 t (1H, CH_2), 2.55 d (2H, CH_2), 7.09 d (1H, 6-H), 7.22 d (1H, 7-H), 7.70 s (1H, 4-H), 8.03 s (1H, 1′-H), 9.7 s (1H, 3′-H) IR spectrum, ν, cm^{-1}: 1620 (C=O); 2210 (C≡N)
XV	35 h, 100°C	88	^{1}H (DMSO-d_6), δ, ppm: 2.32 m (1H, CH_2), 2.54 m (1H, CH_2), 2.75 d (2H, CH_2), 7.44 d (1H, 6-H), 7.55 d (1H, 7-H), 7.77 s (1H, 4-H), 8.35 s (1H, 1′-H), 5.43 s (1H, 1″-H), 9.02 s (1H, 3″-H) IR spectrum, ν, cm^{-1}: 1380 (C=N), 1460 (N=N), 1615 (C=O)
XVII	36 h, 90°C	46	^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.18 m (1H, CH_2), 2.50 m (1H, CH_2), 3.05 d (2H, CH_2), 7.12 d (1H, H_{arom}), 7.45 d (1H, H_{arom}), 7.60 s (1H, H_{arom}), 7.87 s (1H, NH), 9.79 s (1H, NH) ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 29.430 (CH_2), 36.211 (CH_2), 71.204 (C_{quat}), 124.784 (C_{arom}), 124.519 (C_{arom}), 129.940 (C_{arom}), 130.486 (C−Br), 140.751 (C_{arom}), 146.676 (C_{arom}), 156.421 (CO), 176.707 (CO) IR spectrum, ν, cm^{-1}: 1720 (C=O), 1600 (δNH)
XVIII	20 h, 90°C	70	^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.16 m (1H, CH_2), 2.5 m (1H, CH_2), 3.0 t (2H, CH_2), 7.13 d (1H, H_{arom}), 7.25 d (2H, H_{arom}), 7.63 m (1H, H_{arom}), 8.45 s (1H, NH), 10.78 s (1H, NH) ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 29.757 (CH_2), 36.287 (CH_2), 71.820 (C_{quat}), 122.826 (C_{arom}), 125.076 (C_{arom}), 127.040 (C_{arom}), 128.895 (C_{arom}), 141.450 (C_{arom}), 143.607 (C_{arom}), 156.607 (C=O), 177.327 (C=O) IR spectrum, ν, cm^{-1}: 1700 (C=O), 1610 (δNH)

calcined sodium sulfate, the solvent was distilled off, and the residue was distilled under reduced pressure in an argon atmosphere. A fraction with bp 145°C (12 mm) was collected. Yield of **III** 8.23 g (80%), colorless liquid, purity 100% (according to the GLC data); published data [7]: bp 165°C (16 mm).

***m*-Bromobenzyl chloride (IV).** Thionyl chloride, 7.3 ml (0.1 mol), was added dropwise with stirring over a period of 30 min to 6.75 g (0.036 mol) of *m*-bromobenzyl alcohol. The mixture was heated for 2 h (until gaseous products no longer evolved) and was distilled under reduced pressure in an argon atmosphere. A fraction with bp 93°C (4 mm) was collected. Yield 4.76 g (65%), colorless liquid containing 98.04% of the main substance (GLC); published data [7]: bp 104°C (11 mm).

Diethyl *m*-bromobenzylmalonate (V). Diethyl malonate, 10.6 ml (0.07 mol), was added dropwise under argon to a solution of 2.8 g (0.048 mol) of sodium ethoxide in 20 ml of anhydrous ethanol. *m*-Bromobenzyl chloride, 4.76 g (0.023 mol) was then added, and the mixture was kept slightly boiling for 5.5 h. The solvent was distilled off on a rotary evaporator, and ice water was added to the residue until it dissolved completely. The solution was extracted with diethyl ether (3 × 50 ml), and the combined extracts were dried over calcined sodium sulfate and evaporated. Yield 7.3 g (99.2%), colorless liquid contaning 97.44% of the main substance (GLC).

***m*-Bromobenzylmalonic acid (VI).** A solution of 7.3 g (0.022 mol) of diethyl *m*-bromobenzylmalonate (**V**) in 12 ml of ethanol was added dropwise to a solution of 3.2 g (0.08 mol) of sodium hydroxide in 6 ml of water. The mixture was stirred for 5 h on heating, the solvent was distilled off under reduced pressure, and the residue was dissolved in water. The solution was cooled to 0°C, carefully acidified to pH 1 with concentrated hydrochloric acid, and extracted with

5 portions of diethyl ether. The combined extracts were washed with a saturated solution of sodium chloride, dried over calcined sodium sulfate, and evaporated. Yield 6.2 g (100%).

3-(*m*-Bromophenyl)propionic acid (VII). *m*-Bromobenzylmalonic acid (**VI**), 6.2 g (0.022 mol), was placed in a distillation flask and was heated to 170°C under a residual pressure of 30 mm. Vigorous evolution of carbon dioxide was observed. When the decarboxylation was complete, the yellow oily substance was crystallized from hexane. Yield 4.15 g (80%), light brown crystals, mp 74°C [8]. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.66 t (2H, CH_2), 2.95 t (2H, CH_2), 7.12 m (2H, H_{arom}), 7.35 m (2H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 30.10 (CH_2), 35.28 (CH_2), 122.538 (C^5), 126.93 (C^6), 129.54 (C^1), 130.11 (C^2), 131.36 (C^4), 142.38 (C^3), 179.04 (CO).

3-(*m*-Bromophenyl)propionyl chloride (VIII). Thionyl chloride, 0.8 ml (0.011 mol), was added dropwise to 1.28 g (0.0056 mol) of acid **VII**. When the mixture became homogeneous, it was heated until gaseous products no longer evolved. Excess thionyl chloride was distilled off under reduced pressure on heating on a water bath. Dry benzene was added, and thionyl chloride–benzene aseotrope was distilled off under reduced pressure. Yield 1.36 g (96%); purity 96.04% (GLC).

5-Bromoindan-1-one (IX). A solution of 1.36 g (0.0056 mol) of acyl chloride **VIII** in 10 ml of dry methylene chloride was added dropwise to a solution of 0.95 g (0.007 mol) of anhydrous $AlCl_3$ in 3 ml of dry methylene chloride, cooled to –10°C. The mixture was heated on a water bath for 5 h under reflux, poured onto ice, and a small amount of concentrated hydrochloric acid was added (to pH 5). The organic phase was separated, and the aqueous phase was extracted with methylene chloride (2 × 30 ml). The extracts were combined with the organic phase, washed in succession with water, a 2% solution of sodium hydroxide, and water again, dried over calcined sodium sulfate, and evaporated. The residue was recrystallized from heptane. Yield 0.70 g (60%), light yellow crystals, mp 126°C (purity 100%; GLC); published data [9]: mp 125–127°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.69 t (2H, CH_2); 3.14 t (2H, CH_2), 7.52 d (1H, H_{arom}), 7.63 d (1H, H_{arom}), 7.67 s (1H, H_{arom}).

5-Diethoxyphosphinoylindan-1-one (X). An ampule was charged with 0.3 g (0.0014 mol) of 5-bromoindan-1-one, 0.19 g (0.0014 mol) of diethyl hydrogen phosphite, 0.0063 g (2.8×10^{-5} mol) of palladium(II) acetate, 0.015 g (5.6×10^{-5} mol) of triphenylphosphine, 0.032 g (0.14 mmol) of benzyltriethylammonium chloride, and 0.19 g (0.14 mmol) of potassium carbonate. The mixture was heated on a water bath for 6 h at 90°C with occasional stirring. It was then passed through a chromatographic column using chloroform–petroleum ether (3:1) as eluent. Yield 0.16 g (43%). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.20 t (6H, CH_3), 2.59 t (2H, CH_2), 3.07 t (2H, CH_2), 4.02 m (2H, OCH_2), 7.84 d (1H, H_{arom}), 7.68 d (1H, H_{arom}), 7.63 d (1H, H_{arom}). ^{31}P NMR spectrum ($CHCl_3$): δ_P 17.3 ppm, s.

1-Oxoindan-5-carbonitrile (XI). A solution of 0.5 g (0.0024 mol) of 5-bromoindan-1-one (**IX**) and 0.52 g (0.0027 mol) of copper(I) cyanide in 1 ml of DMF was stirred for 6 h on heating under reflux. A 10% aqueous solution of ammonia, 10 ml, was added, and the precipitate was filtered off, washed repeatedly with an ammonia solution on a filter, and dried. Yield 0.2 g (55%). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.75 t (2H, CH_2), 3.16 t (2H, CH_2), 7.75 d (1H, H_{arom}), 7.85 d (1H, H_{arom}), 8.14 s (1H, H_{arom}).

5-(1*H*-Tetrazol-5-yl)indan-1-one (XII). A solution of 0.2 g (0.0013 mol) of 1-oxoindan-5-carbonitrile, 0.12 g (0.0017 mol) of sodium azide, and 0.1 g (0.0017 mol) of ammonium chloride in 2.5 ml of DMF was stirred for 24 h at 120°C. The mixture was evaporated, the residue was washed with cold water (2 × 20 ml) and acidified to pH 2 with hydrochloric acid, and the solid residue was washed with water (3 × 20 ml) and ether (2 × 15 ml), dried for 2 h at 80°C in a drying box, and recrystallized from acetone. Yield 0.24 g (92%). ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 2.84 t (2H, CH_2), 3.00 t (2H, CH_2), 7.71 d (1H, H_{arom}), 7.81 d (1H, H_{arom}), 8.10 s (1H, H_{arom}), 9.23 s (1H, NH).

1-Indanone (XVI). A solution of 21.2 g (0.21 mol) of chromium(VI) oxide in 80 ml of acetic acid and 35 ml of water was added with stirring to a solution of 10 g (0.086 mol) of indan in 40 ml of acetic acid at such a rate that the temperature did not exceed 20°C. The mixture was stirred for 16 h, 180 ml of water was added, and the mixture was extracted with ether (3 × 70 ml). The extract was dried over calcined sodium sulfate and evaporated, and the residue was distilled under reduced pressure. A fraction with bp 120°C (10 mm) was collected. Yield 5.62 g (50%), mp 42°C; published data [10]: mp 40–42°C [10]. The purity of the product was 100% (GLC).

General procedure for preparation of hydantoins XIII–XV, XVII, and XVIII. 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 1-indanone in 3 ml of DMF, and the mixture was heated until the reaction was complete. It was then cooled, 50 ml of ethyl acetate was added, and the mixture was washed with 60 ml of water. The product was extracted into a 30% solution of NaOH (60 ml). The aqueous phase was separated and acidified to pH 5 with hydrochloric acid. The acid solution was extracted with ether (3×50 ml), the combined organic extracts were dried over calcined sodium sulfate and evaporated, and the residue was recrystallized from benzene. The reaction conditions (temperature and time) and yields and spectral parameters of the products are given in table.

REFERENCES

1. Matveeva, E.D., Podrugina, T.A., Zefirova, O.N., Alekseev, A.S., Bachurin, S.O., Pellicciari, R., and Zefirov, N.S., *Russ. J. Org. Chem.*, 2002, vol. 38, no. 12, pp. 1764–1768.
2. Ma, D., Tian, H., Sun, H., Kozikowski, A.P., Pshenichkin, S., and Wroblewski, J.T., *Bioorg. Med. Chem. Lett.*, 1997, vol. 7, no. 9, pp. 1195–1198.
3. Kabachnik, M.M. and Solntseva, M.D., *Izv. Ross. Akad. Nauk, Ser. Khim.*, 1997, no. 8, pp. 1556–1557.
4. Ellis, P. and Romney-Alexander, T., *Chem. Rev.*, 1987, vol. 87, no. 4, pp. 779–794.
5. Katritzky, A., Aslan, I.D., Shcherbakova, I.A., Chem, J., and Beliakov, S.A., *J. Heterocycl. Chem.*, 1996, vol. 33, no. 4, pp. 1107–1114.
6. Mauger, A.B. and Ross, W.C.J., *Biochem. Pharmacol.*, 1962, vol. 11, pp. 847–858.
7. Mettler, C., *Ber.*, 1905, vol. 38, p. 2809.
8. Mettler, C., *Ber.*, 1905, vol. 38, p. 1622.
9. Ma, D., Tian, H., and Zou, G., *J. Org. Chem.*, 1999, vol. 64, no. 1, pp. 120–125.
10. Cope, A.C. and Field, L., *J. Am. Chem. Soc.*, 1949, vol. 71, no. 5, pp. 1589–1593.