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One-Pot Synthesis of Phenytoin Analogs*

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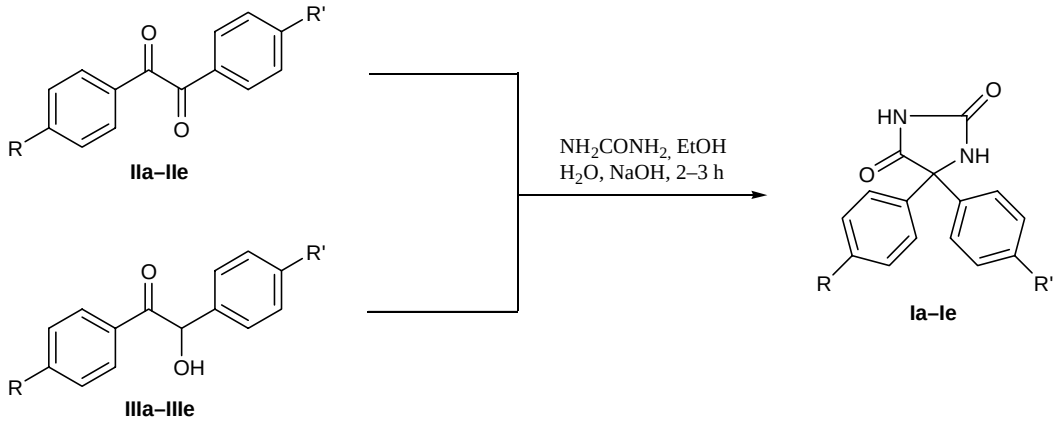
Abstract—A series of phenytoin analogs (5,5-diphenylimidazolidine-2,4-dione or 5,5-diphenylhydantoin) were synthesized in 65–75% yield from the corresponding substituted benzils. The same products were also obtained directly from α-hydroxy ketones via one-pot procedure.

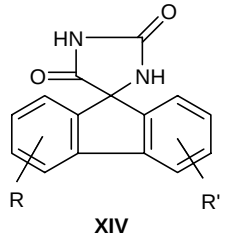
5,5-Diphenylimidazolidine-2,4-dione or 5,5-diphenylhydantoin (PHT) is an antiepileptic drug [1]. In the recent publication [2], the design and synthesis of new antiepileptic targets for neuronal voltage-sensitive sodium channel (NVSC) have been extensively considered. Study of these model hydantoin derivatives could provide an important knowledge and predict how to enhance binding site to NVSC [3]. Structural information about phenytoin binding site is scanty [3]. The exact location of these sites and structure requirements for optimal binding have not yet been determined. According to the results of recent studies, 5,5-diphenylhydantoin inhibits binding of human immunodeficiency virus (HIV) to lymphocytes [4], affects hepatic thyroxine [5], selectively enhances vincristine cytotoxicity [6], affects myocardial contractivity and hemodynamics [7], and reduces pesticide residue in human adipose tissue [8].

In the present article specific attention is given to the novel synthesis of phenytoin analogs. The

Scheme 1.



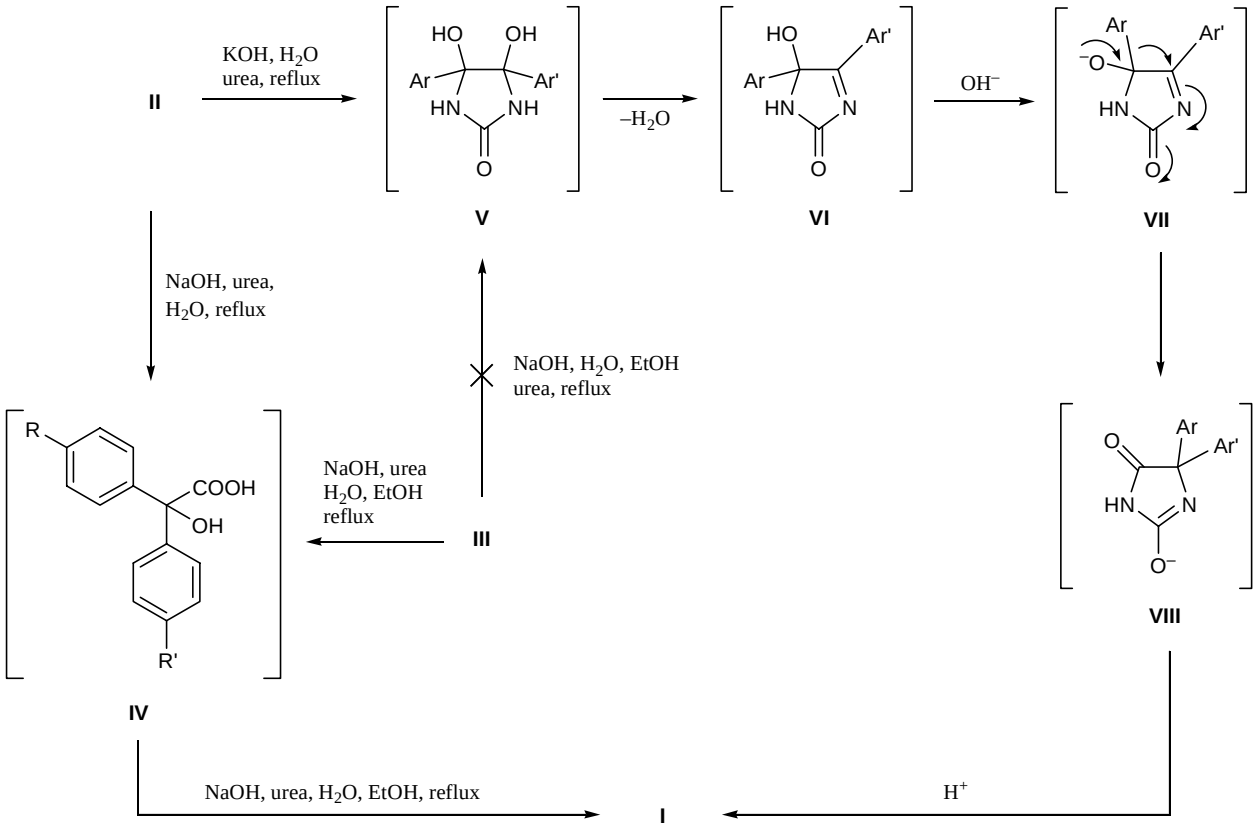
I–III, R = R' = H (**a**), R = R' = Me (**b**), R = Me_2N, R' = H (**c**), R = R' = MeO (**d**), R = MeO, R' = H (**e**).



XIV

* The original article was submitted in English.

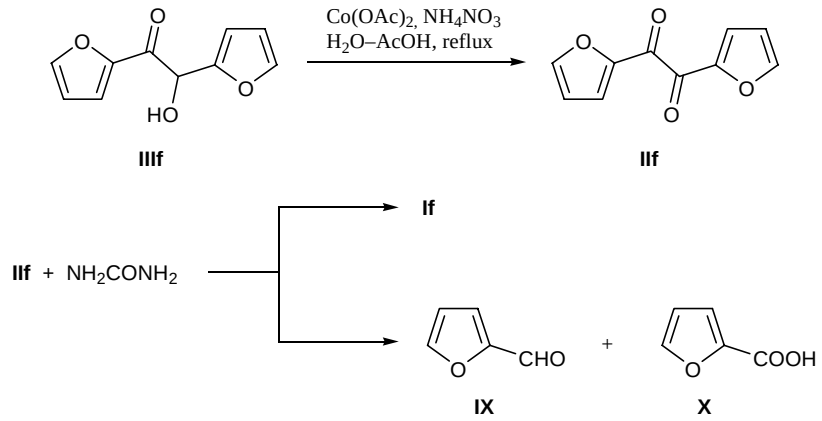
Scheme 2.



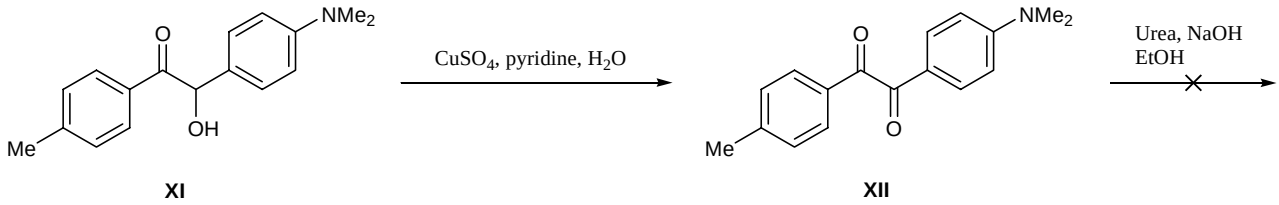
Bucherer–Bergs procedure is one of the general methods which are usually used for the synthesis of hydantoin [9, 10], in particular for the preparation of 5-substituted hydantoin derivatives containing a non-aromatic or one phenyl group [2]. Several procedures for the synthesis of new hydantoin-like compounds were described previously [10–16]. However, a few studies have been reported on the preparation of unsymmetrically substituted hydantoins, e.g., **Ic** and **Ie**, and almost no published data are available on the synthesis of spiro hydantoins like **XIV** [17a].

Some symmetrical and unsymmetrical α-diketones, such as **IIa**–**IIf** and **XII**, were prepared from the corresponding α-hydroxy ketones **IIIa**–**IIIf** and **XI** by oxidation with ammonium nitrate in the presence of copper(II) acetate in acetic acid (Scheme 3) according to the known procedure [18]. Compound **XI** was oxidized with $CuSO_4$ in pyridine [19]. Initial

Scheme 3.



Scheme 4.



XI **XII**

α-hydroxy ketones were obtained by the benzoin condensation [20]. We recently reported on enantio-, regio-, and stereoselective reduction of several α-diketones and aliphatic, aromatic, and prochiral β-diketones and β-keto esters in the presence of *S. Cerevisiae* [17b, 17c]. The yields, melting points, and spectral parameters of the synthesized compounds are collected in table. One-pot reactions of substituted benzils **IIa–IIf** and **XII** or benzoins **IIIa–IIIf** and **XI** with urea in aqueous ethanol in the presence of sodium hydroxide afforded the desired phenytoin derivatives **Ia–Ie** in 65–75% yield (Scheme 1).

Scheme 2 shows the generally accepted mechanism of the transformation of benzoins **III** into diarylhydantoins **I**. Benzilic acid **IV** could be formed as intermediate by the action of NaOH and urea on compounds **II** and **III** in aqueous ethanol. The synthesis of benzilic acid from benzoin was reported in [25]. On the other hand, the condensation of benzoin with urea is known to afford 4,5-diphenyl-2,3-dihydro-1*H*-imidazol-2-one. We have still no rigorous proofs that acid **IV** is the key intermediate in the formation of 5,5-diphenylhydantoin. The main difference between the proposed mechanism (see intermediates **IV**–**VIII** in Scheme 2) and those reported in [22, 26] consists of facile rearrangement of initially formed benzilic acid, followed by hydantoin ring closure. There is some analogy between the benzoin–benzilic acid rearrangement and migration of the aryl group in intermediate product **VII** by the action of alkali, which was reported in [27, 28].

We failed to obtain the corresponding substituted hydantoin **If** by condensation of furil **IIf** with urea in alkaline solution (Scheme 3). Under these conditions, rearrangement of **IIf** into furilic acid (by analogy with the transformation of benzil into benzilic acid [29]) did not occurr, and the products were 2-furaldehyde **IX** and 2-furoic acid **X** (Scheme 3).

Likewise, purified 1-(4-dimethylaminophenyl)-2-*p*-tolylethane-1,2-dione (**XII**) failed to react with urea and NaOH in aqueous ethanol under reflux (reaction time 7–8 h). After appropriate treatment, we isolated unchanged initial compound **XII** (Scheme 4). Under analogous conditions, dimethylamino-substituted benzoin **XI** was completely converted into benzil **XII**.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on Bruker FT 80 MA_2 and Bruker DRX 500 Avance spectrometers from solutions in $CDCl_3$, acetone-d_6, or DMSO-d_6 using tetramethylsilane as internal reference. The IR spectra were measured on a Shimadzu Model 470 instrument. The high-resolution mass spectra were obtained on a Fisons Trio-1000 mass spectrometer. The melting points were determined using a Mettler Fp5 melting point apparatus and are uncorrected. The yields refer to products purified by recrystallization or by column or thin-layer chromatography (central cuts). The products were identified by comparing their NMR and IR spectral data (see table), GLC and TLC parameters, and melting points with those of authentic samples.

2-Hydroxy-l,2-di-*p*-tolylethanone (IIIb). A 250-ml round-bottom flask was charged with 50 ml of 96% ethanol and 30 ml (30.9 g, 25 mmol) of *p*-methylbenzaldehyde (purified by vacuum distillation), a solution of 2.5 g (38.3 mmol) of KCN in 25 ml of distilled water was added, and the mixture was stirred for 3 h on heating under reflux. The progress of the reaction was monitored by TLC. The unreacted initial aldehyde was removed by steam distillation. The orange oily liquid was dissolved in 30 ml of ethanol, and the solution was left to stand for crystallization. The crude product was repeatedly (3–4 times) crystallized from 96% ethanol. Yield 16.5 g (55%), white powder, mp 86–88°C; published data [24]: mp 86–88°C.

1,2-Di-*p*-tolyl-1,2-ethanedione (IIb). A 250-ml round-bottom flask was charged with 10 g (40 mmol) of compound **IIIb**, 0.3 g (1.5 mmol) of $Cu(OAc)_2 \cdot H_2O$, 10 g (125 mmol) of ammonium nitrate, and 60 ml of 80% acetic acid. The mixture was heated at the boiling point for 2 h with stirring. The solution was cooled, and the precipitate was filtered off, dissolved

Yields, melting points, and IR and NMR spectra of compounds **I**–**III**, **VI**, and **VII**

Comp. no.	Yield, %	mp, °C (solvent)	IR spectrum (KBr), ν, cm^{-1}	^1H and ^{13}C NMR spectra, δ, δ_C, ppm
Ia	75	292 (96% EtOH); 286–295 [21]	3270 s, 3200 s, 1770 s, 1720 s, 1710 s	^1H (DMSO): 7.2 m (10H), 8.9 s (1H), 10.7 s (1H) ^{13}C (DMSO): 75.5 126, 128.4, 129, 143, 160, 170.7
Ib	68	228 (96% EtOH); 230 [22]	3200 s, 1720 s	^1H (DMSO): 2.5 s (6H), 3.5 s (H_2O), 7.4 s (8H), 9.3 s (1H), 11.2 s (1H); DMSO–D_2O: 2.1 s (6H), 4 s (H_2O), 7.2 s (8H) ^{13}C (DMSO): 20.9, 75.4, 128.3, 129.7, 135.1, 140, 160, 170.6
Ic	65	229 (96% EtOH)	3300 s, 3200 s, 1760 s, 1720 s, 1700 s	^1H (DMSO): 2.8 s (6H), 3.2 s (H_2O), 6.6 d (2H), 7 d (2H), 7.4 s (5H), 9 s (1H), 10.7 s (1H); DMSO–D_2O: 2.9 s (6H), 4.2 s (H_2O), 6.8 d (2H), 7.2 d (2H), 7.5 s (5H) ^{13}C (DMSO): 43.5, 75.5, 113.6, 126, 128.4, 129, 129.3, 132.5, 142, 143, 160, 170.5
Id	–	225	3200 s, 1720 s	^1H (DMSO): 3.8 s (6H), 6.8 d (4H), 7.2 d (4H), 9 s (1H), 10.8 s (1H) ^{13}C (DMSO): 56, 75.6, 114.5, 129.3, 135.3, 159.6, 160, 170.7
Ie	65	222	3300 s, 3200 s, 1720 s, 1700 s	^1H ($CDCl_3$): 1.5 s (H_2O), 3.7 s (3H), 7 m (9H) ^{13}C ($CDCl_3$): 56, 75.4, 114.6, 126, 128.4, 129, 129.4, 135.3, 143, 159.4, 160, 170.7
IIa	90	93 (96% EtOH); 95 [23]	3070 w, 1650 s	^1H ($CDCl_3$): 7.5 m (6H), 8 d.d (4H) ^{13}C ($CDCl_3$): 129, 130, 133, 135, 195
IIb	71	103 (96% EtOH); 102–104 [24]	1660 s	^1H ($CDCl_3$): 2.3 s (6H), 7.2 d (4H, J = 8.2 Hz), 7.7 d (4H, J = 8.2 Hz) ^{13}C ($CDCl_3$): 22, 130, 130.1, 131, 146, 194
IIc	80	114–116 (96% EtOH)	1675 s, 1630 s	^1H ($CDCl_3$): 3 s (6H), 6.6 d (2H), 7.5 m (3H), 7.9 m (4H) ^{13}C ($CDCl_3$): 40, 111, 121, 129, 130, 132, 134, 134.5, 154, 192, 196
IId	71	102–104 [24]	3460 m, 1650 s	^1H ($CDCl_3$): 2.3 s (6H), 7.2 d (4H, J = 8.2 Hz), 7.7 d (4H, J = 8.2 Hz) ^{13}C ($CDCl_3$): 22, 130, 130.1, 131, 146, 194
IIe[a]	75	66	1650 s, 1585 s	^1H ($CDCl_3$): 4 s (3H), 7.1 d (2H), 7.7 m (3H), 8.1 d (4H) ^{13}C (CD_3COCD_3, 125 MHz): 54.9, 114.1, 125.5, 128.7, 129, 131.6, 132.8, 134.4, 164.8, 192.8, 194.6
IIf	75	166 (96% EtOH); 165–166 [23]	1640 s	^1H ($CDCl_3$): 6.7 d.d (2H), 7.7 d.d (2H), 7.8 d.d (2H)
IIIa	88	137 (96% EtOH) [23]	3400 s, 1665 s	^1H ($CDCl_3$): 4.6 d (1H), 6 d (1H), 7.4 m (8H), 8 d (2H) ^{13}C ($CDCl_3$): 75.4, 128, 129, 129.1, 129.3, 129.6, 133, 134, 139, 199
IIIb	55	86–88 (96% EtOH) [24]	3450 s, 1670 s	^1H ($CDCl_3$): 2.3 s (3H), 2.4 s (3H), 4.7 d (1H), 7.2 m (6H), 7.9 d (2H) ^{13}C ($CDCl_3$): 21, 21.4, 75, 127, 129, 130, 130.2, 137.6, 138, 144, 198
IIIc	40	162 (96% EtOH); 161–163 [19b]	3400 s, 1650 s, 1600 s	^1H ($CDCl_3$): 2.9 s (6H), 4.7 d (1H, J = 6.1 Hz), 5.8 d (1H, J = 6.1 Hz), 6.5 d (2H, J = 9.1 Hz), 7.2 m (5H), 7.8 d (2H, J = 9.1 Hz) ^{13}C ($CDCl_3$, DMSO): 39, 75, 110, 120.4, 127, 127.2, 128, 131, 140.6, 153, 196

Table. Contd.

Comp. no.	Yield, %	mp, °C (solvent)	IR spectrum (KBr), ν, cm^{-1}	^1H and ^{13}C NMR spectra, δ, $δ_C$, ppm
IIId	54	109 (96% EtOH); 109–110 [24]	3450 s, 1670 s, 1600 s	^1H ($CDCl_3$): 2.3 s (3H), 2.4 s (3H), 4.7 d (1H), 6 d (1H), 7.2 m (6H), 7.9 d (2H) ^{13}C ($CDCl_3$): 21, 21.5, 75, 127, 129, 130, 130.1, 131, 137.5, 138, 144, 198
IIIe	21	106 (96% EtOH); 105–106 [19b]	3460 m, 1650 s, 1600 s	^1H ($CDCl_3$, 80 MHz): 3.9 s (3H), 4.7 d (1H, *J* = 6 Hz), 6 d (1H, *J* = 6 Hz), 7 d (2H, *J* = 9 Hz), 7.4 m (5H), 8 d (*J* = 9 Hz) ^{13}C (CD_3COCD_3, 125 MHz): 54.6, 75.2, 113.3, 126.5, 127, 127.4, 128.2, 130.9, 140.1, 163.5, 197
IIIf	45	139 (96% EtOH); 138–139 [23]	3400 s, 1665 s	^1H ($CDCl_3$): 4.2 d (1H), 5.8 d (1H), 6.4 d.d (2H), 6.6 d.d (1H), 7.3 d.d (1H), 7.4 d.d (1H), 7.6 d.d (2H), 7.7 d.d (2H)
VI	45	120 (96% EtOH)	3400 s, 1670 s	^1H ($CDCl_3$): 2.4 s (3H), 3.2 s (6H), 4.9 d (1H), 6 d (1H), 6.8 d (2H), 7.4 m (4H), 8 d (2H)
VII	78	125	3430 s, 1600 s	^1H ($CDCl_3$): 2.4 s (3H), 3.1 s (6H), 6.6 d (2H), 7.2 d (2H), 7.8 m (4H)

[a] Found: M^+ 240.0789; calculated: *M* 240.0783.

in 96 ethanol, and recrystallized with addition of charcoal. Yield 7.1 g (71%), pale yellow crystals, mp 103°C; published data [24]: mp 102–104°C.

2-Hydroxy-1-(4-methoxyphenyl)-2-phenylethanone (IIIe). A 250-ml round-bottom flask was charged with 24.3 ml (27.2 g, 0.2 mol) of *p*-methoxybenzaldehyde (purified by vacuum distillation), 22.2 ml (23.3 g, 0.22 mol) of freshly distilled benzaldehyde, 100 ml of 96% ethanol, and a solution of 5 g (77 mmol) of KCN in 30 ml of water. The mixture was heated for 3 h at the boiling point under vigorous stirring using a magnetic stirrer. When the mixture warmed up to the boiling point, it became homogeneous. The unreacted aldehydes and ethanol were removed by steam distillation. The orange oily liquid was dissolved in 50 ml of hot ethanol, and the solution was left to stand for crystallization. The crude product was a mixture of benzoin and compound **IIIe**. Fractional crystallization from 96% ethanol gave 10.2 g (21%) of compound **IIIe** as colorless crystals with mp 106°C; published data [19a]: mp 105–106°C. The product was repeatedly crystallized until its melting point (105°C) no longer changed.

1-(4-Methoxyphenyl)-2-phenyl-1,2-ethanedione (IIe). A 250-ml round-bottom flask was charged with 6 g (25 mmol) of compound **IIIe**, 0.3 g (1.5 mmol) of $Cu(OAc)_2 \cdot H_2O$, and 9 g (112 mmol) of ammonium nitrate, and 70 ml of 80% (by volume) aqueous acetic acid was added. The mixture was heated for 3 h at the boiling point under stirring. It was then cooled, and the precipitate was filtered off, dissolved in 96% ethanol, and recrystallized. Yield 4.5 g (75%), yellow crystals, mp 66°C.

1-(4-Dimethylaminophenyl)-2-phenyl-1,2-ethanedione (IIc). Compound **IIIc** was synthesized as described above for **IIIe**. A 250-ml round-bottom flask was charged with 14 g (56 mmol) of $CuSO_4 \cdot 5H_2O$, 40 ml (39.2 g, 496 mmol) of pyridine, and 30 ml of distilled water. The mixture was heated on a water bath with stirring until it became homogeneous, 5.38 g (20 mmol) of compound **IIIc** was added, and the mixture was refluxed for 2 h under stirring. The mixture was cooled, and the crude product was filtered off, washed with water, and recrystallized from 96% EtOH. Yield 4.19 g (78%), yellow crystals, mp 125°C.

5,5-Di-*p*-tolylimidazolidine-2,4-dione (Ib). A 100-ml round-bottom flask equipped with a reflux condenser was charged with 5.95 g (25 mmol) of compound **IIb**, 3 g (50 mmol) of urea, 15 ml of 40% aqueous NaOH, and 70 ml of 96% ethanol. The mixture was heated for 3 h under reflux with stirring, cooled to room temperature, and poured into 120 ml of distilled water. The resulting mixture was vigorously stirred for 15 min, and the precipitate was filtered off, and recrystallized from 96% ethanol. Yield 2.41 g (62%), colorless crystals, mp 225°C.

5-(4-Methoxyphenyl)-5-phenylimidazolidine-2,4-dione (Ie). A 100-ml round-bottom flask equipped

with a reflux condenser was charged with 3 g (12.5 mmol) of compound **IIIe**, 1.5 g (25 mmol) of urea, 9 ml of 30% aqueous NaOH, and 40 ml of 96% ethanol. The mixture was heated for 3 h under reflux with stirring, cooled to room temperature, and poured into 60 ml of distilled water. The resulting mixture was vigorously stirred for 15 min and filtered, and concentrated hydrochloric acid was added to the filtrate (on cooling with ice) to strongly acidic reaction. The colorless precipitate was filtered off and recrystallized from 96% ethanol. Yield 2.51 g (65%), colorless crystals, mp 222°C.

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