ACETALS OF ACID LACTAMS AND AMIDES. 70.* REACTIONS OF 2-AMINOMETHYLENEINDOLIN-3-ONE WITH CH-ACIDS. SYNTHESIS OF SUBSTITUTED PYRROLO[1,2-*a*]INDOLES

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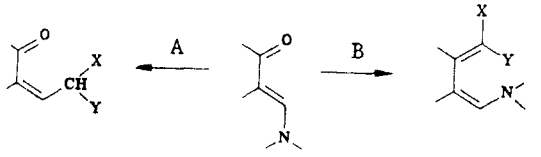
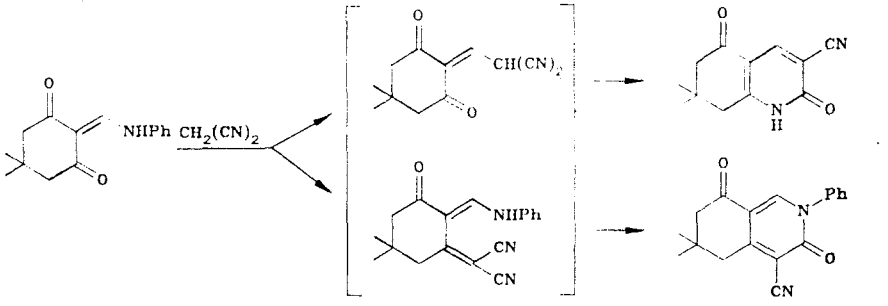
The reaction of enaminoketones, 2-dimethylamino- and piperidinomethyleneindolin-3-ones with dimedone and Meldrum acid, gave the corresponding cyclic derivatives of 2-vinylindolin-3-one, while with cyanoacetic ester and cyanoacetamide — the derivatives of 3-amino-9-oxopyrrolo[1,2-a]indole were obtained.

It has previously been shown [2, 3] that in the reaction of 1-acetylindoxyl with DMFA and N-formylpiperidine diethylacetals the corresponding enaminoketones Ia, b are formed. Certain transamination and acylation reaction of the latter were studied.

The present work is devoted to the investigation of the condensation of compounds Ia, b with various CH-acids. The reaction of enaminoketones with compounds having an active methylene unit may proceed in two directions — with the participation at the first stage of a carbonyl or an enamine fragment.



It has been shown in several papers [4-7] that these processes may proceed in parallel, or one of them may be preferential, but this problem has not been examined in detail in the literature. As an example of the parallel occurrence of condensations **A** and **B**, we can cite the reaction of 2-(anilinomethylene)dimedone with malononitrile [4].



The reaction of anaminoketone Ia with dimedone (II) or the Meldrum acid (III) leads to the formation of compounds, which could have a structure of 2-vinyl-3-hydroxyindole IV, V derivatives (path A) or, taking into account the above-cited literature data, the structure of type VI (path B).†

*For Communication 69, see [1].

†The hydrolysis of the enamino grouping may proceed due to the water liberated in the course of this reaction.

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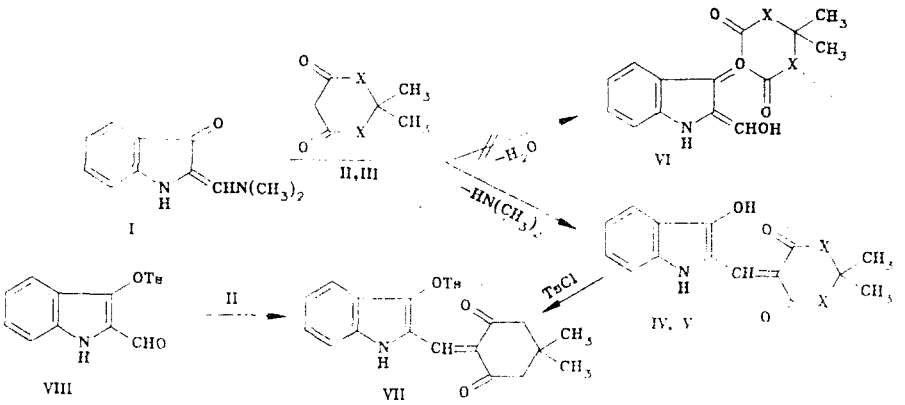
TABLE 1

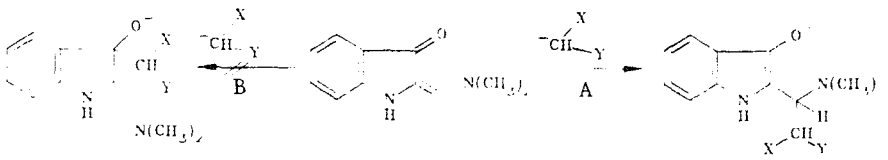
Starting compound	Reagents, mole		Yield, %	
	tri-ethyl-amine	piper-idyl-amine	IXa	Xa
Ia	2	—	74	—
Ib	1	—	44	27
Ib	—	2	34	32
Ib	—	4	—	87

The structure of compounds IV, V obtained as derivatives of 2-vinylindole was established using compound IV, which in the reaction with *p*-toluenesulfonyl chloride was converted into the tosyloxy derivative VII. The latter compound was also obtained by a countersynthesis from 2-formyl-3-tosyloxyindole (VIII) [3] with dimedone

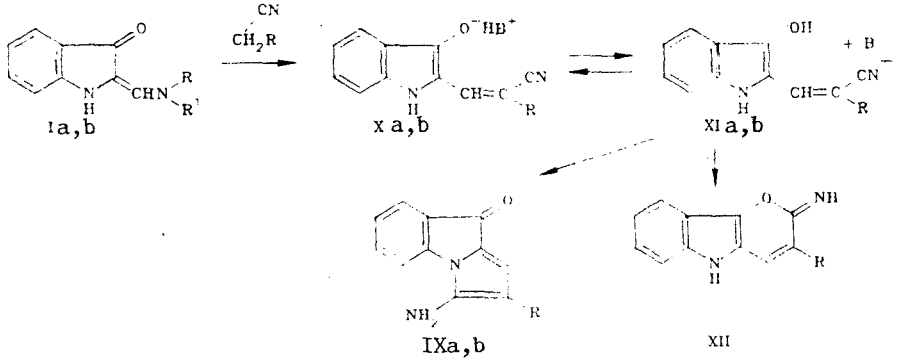


II X=CH_2; III X=O

Hence, in this case, at the first stage the anion of the CH-acid adds at the 2′-position of the enamine fragment with subsequent splitting of dimethylamine. This undoubtedly is enhanced by the fact that an aromatic indole system is formed during such an addition:



We should note that a similar attack with the formation of an anion-radical of the aromatic system is observed during the electrochemical reduction of enaminoketones I [8]. At the same time, path B (the addition at the carbonyl group) is energetically unfavorable, since it is accompanied by an $sp^2 \rightarrow sp^3$ hybridization of the carbon atom included into the five-membered ring [9].

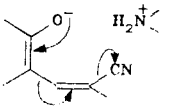


I a R=R′=CH_3, b R+R′=$(CH_2)_5$; IX, X, XI a R=$COOC_2H_5$, b R=$CONH_2$; Xa,b
B=$(CH_3)_2NH$, $(C_2H_5)_3N$, piperidyl

We also studied the reaction of anaminoindolinones Ia, b with derivatives of cyanoacetic acid (ethyl ester, amide and benzyl amide) in boiling benzene. It was found that the reaction of compound Ia with a twofold excess of the cyanoacetic ester is possible only in the presence of a base (for example triethylamine), and the end product

of the reaction is 2-ethoxycarbonyl-3-amino-9-oxopyrrolo[1,2-*a*]indole (IX).* When enaminoketone Ib was used in this reaction, the salt of piperidine with the ethyl ester of α-cyano-β-(3-hydroxyindol-2-yl)acrylic acid (Xa) was isolated together with pyrroloindole IXa. Compound Xa was previously obtained by us from 1-acetyl-3-acetoxy-2-formylindole [3].

At the first stage of the reaction of enaminoketones Ia, b with cyanoacetic ester, salts of α-cyano-β-(3-hydroxyindol-2-yl)acrylic esters (Xa) are formed. Since these are salts of fairly weak acids they undergo thermal decomposition with the formation of the corresponding amines and a derivative of indolyl acrylic ester XIa. During this reaction the dissociation is realized to a greater extent the less the amount of strong amine present in the reaction mixture, and the greater the amount of the amine removed in the course of the reaction. It should be noted that pyrrole cyclization of compound XIa then proceeds as the result of electrophilic attack of the carbon atom of the cyano group on the indole nitrogen atom, and in the case of an anion of type

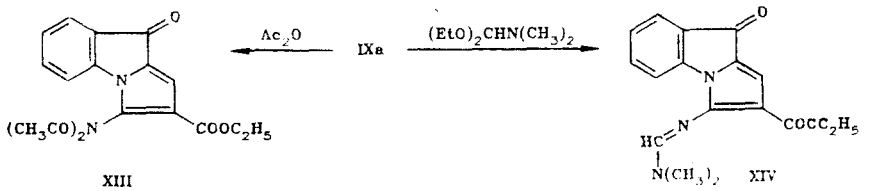


it becomes less probable because of a decrease in the electrophilicity of this group due to an electron-donor effect of the anionic fragment. When the enaminoketone Ia is used, the liberated dimethylamine is removed from the boiling reaction mixture and the process shifts in the direction of the formation of the tricyclic compound IXa. However, in the presence of a higher-boiling piperidine in the reaction mixture (in the case of the enaminoketone Ib), this shift of the equilibrium cannot be accomplished, and the tricyclic compound IXa, is formed during that period in a smaller amount. Replacement of triethylamine by piperidine leads to a decrease in the degree of cyclization and with a large excess of it, salt Xa can be isolated in a high yield (Table 1). Increase in the reaction time (which in principle should lead to increase in the degree of cyclization), is impossible because of resinification due to polymerization processes.

It should be noted that the cyclization of compound XIa with the participation of a cyano group is possible both at the indole nitrogen atom and at the hydroxy group. In this case the reaction product will be pyrano[2,3-b]indole XII.

The structure of the tricyclic compound IXa was confirmed by the PMR spectral data in which, besides the signals of the aromatic protons and the ethoxycarbonyl group, there is a broad signal in the 7.41 ppm region, characteristic for the NH_2 group protons, while at 7.04 ppm there is a singlet signal of the 1-H proton. In [10] a PMR spectrum of 2-methyl-9-oxopyrrolo[1,2-*a*]indole is given, in which the signal of the corresponding proton is present at 6.84 ppm. Moreover, the structure of compound IXa was confirmed by the formation of diacetylaminopyrroloindole XIII when compound IXa was boiled in acetic anhydride in the presence of sodium acetate.

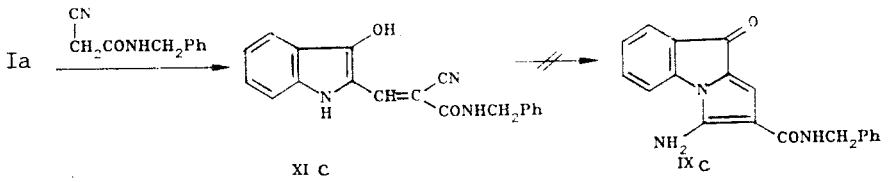
In the PMR spectrum of this compound there is a singlet six-proton signal at 2.40 ppm, which confirms the presence of two equivalent acetyl groups in it. Heating of the tricyclic compound IXa in DMFA acetal gives amidine XIV, in the IR spectrum of which absorption bands at 1700 (COOEt), 1660 (C=O), and 1600 cm^{-1} (C=N, C=C) are observed. In the PMR spectrum the signals of the 1-H proton and the aminomethylene proton are present at 7.09 and 8.48 ppm, respectively.



XIII XIV

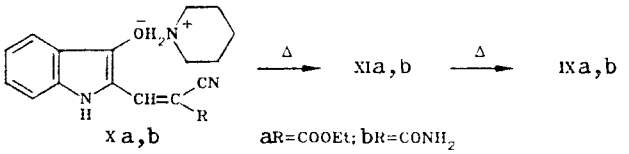
The reaction of compound Ia with cyanoacetamide proceeds similarly to the reaction with cyanoacetic ester, but is accompanied by strong resinification, as a result of which 2-carbamoyl-3-amino-9-oxopyrrolo[1,2-*a*]indole was isolated (IXb) in a 14% yield only. The reaction of compound Ia with cyanoacetic acid benzylamide does not give a cyclic compound, but stops at the stage of formation of a benzylamide of α-cyano-β-(3-hydroxyindol-2-yl)acrylic acid (XIc).

*The presence of the cyclic compound is indicated by the absence in the IR spectrum of an absorption band at 2200 cm^{-1} characteristic for the C=N groups.



In the IR spectrum of amide XIc absorption bands are observed at 3460, 3340 (OH, NH), 2180 (C≡N), 1635 (C=O), and 1625 cm^{-1} (C=C).

In view of the fact that pyrroloindoles IXa, b are formed as the result of a thermal cyclization of derivatives XIa, b, the piperidine salts Xa, b may possibly also undergo thermal cyclization, but at a higher temperature than the boiling point of benzene. In fact, when a solution of salt Xa was boiled in toluene for 30 min, pyrroloindole IXa was formed in a 40% yield. Salt Xb [3] does not dissolve in boiling toluene and, therefore, the time of synthesis of compounds IXb increases to 16 h while the yield of the pure compound is not more than ~2%, which is due to the strong resinification of the reaction mixture.



It is of interest to note than 30 min after the beginning of boiling salt Xb in toluene a yellow material appears in the reaction mixture together with the red-colored starting compound. This compound was isolated and, according to the IR and PMR spectra which are similar to the spectra of compound XIc,* it has been concluded that its structure corresponds to compound XIb. This fact confirms the proposed scheme of formation of tricyclic compounds IX from enaminoindolinones I.

EXPERIMENTAL

The IR spectra were obtained on a Perkin—Elmer 457 spectrophotometer in mineral oil, the mass spectra on a Varian MAT-112 mass spectrometer, with direct introduction of the sample into the ion source. The energy of the ionizing electrons was 70 eV and the temperature of the ionization chamber 180°C. The PMR spectra of the compounds in DMSO-D_6 were recorded on a Varian XL-200 spectrometer, using TMS as an internal standard. The course of the reactions and the purity of the compounds were monitored by TLC on a Silufol UV-254 plate in a 10:1 chloroform—methanol system.

The data of the elemental analysis correspond to the calculated values.

5,5-Dimethyl-2-(3-hydroxyindol-2-ylmethylene)cyclohexane-1,3-dione (IV, $C_{17}H_{17}NO_3$). A mixture of 3.76 g (20 mmoles) of enaminoketone Ia, 5.6 g (40 mmoles) of dimedone II, and 200 ml of benzene was boiled with stirring for 3 h. The mixture was allowed to stand overnight at 20°C. The precipitate that separated out was filtered off and washed with benzene and ether. Yield 2 g. The mother liquor was evaporated. The residue was dissolved in 100 ml of isopropanol, 20 ml of 1 N HCl was added, the mixture was stirred at 20°C for 5 h and allowed to stand overnight. The precipitate that separated out was filtered off, washed with isopropanol and ether. IR spectrum: 3180-2500, 1620, 1580 cm^{-1}. M^+· 283. PMR spectrum: 1.48 (6H, s, $2CH_3$), 2.54 (4H, s, $2CH_2$), 6.90-7.88 (5H, m, CH, arom. protons), 10.75 ppm (1H, br.s, NH). Yield 0.9 g. Overall yield 2.9 g (51%). Mp 180°C (dec., from dioxane).

5,5-Dimethyl-2-(3-hydroxyindol-2-ylmethylene)-1,3-dioxane-4,6-dione (V, $C_{15}H_{13}NO_5$). A mixture of 3.75 g (20 mmoles) of enaminoketone Ia, 5.76 g (40 mmoles) of Meldrum acid III, and 150 ml of isopropanol was stirred for 6 h at 20°C. The precipitate that separated out was filtered off and washed with isopropanol and ether. Yield 1.4 g. A 10-ml portion of 6 N HCl was added to the mother liquor, and the mixture was stirred for 30 min. The precipitate that separated out was filtered off and washed with isopropanol and ether. Mp >210°C (dec., from dioxane). IR spectrum: 3280-2500, 1710, 1660, 1630 cm^{-1}. M^+· 287. PMR spectrum: 1.73 (6H, s, $2CH_3$), 6.98-7.91 (4H, m, CH, arom. protons), 8.42 ppm (1H, s, CH), 10.86 ppm (1H, br.s, NH). Yield 2.58 g. Overall yield 3.98 g (70%).

*We were unable to obtain an analytically pure sample of XIb.

5,5-Dimethyl-2-(3-tosyloxyindol-2-ylmethylene)cyclohexane-1,3-dione (VII, $C_{24}H_{23}NO_3S$). A. A mixture of 0.63 g (2 mmoles) of 2-formyl-3-tosyloxyindole [3], 0.42 g (3 mmoles) of dimedone, and 0.3 ml (2 mmoles) of triethylamine in 10 ml of benzene was allowed to stand for 24 h at 20°C. The mixture was filtered through an SiO_2 layer and washed with ~200 ml of benzene. Benzene was evaporated, and the residue was crystallized from 2-propanol. Mp 158-159°C. IR spectrum: 3700-3100, 1690, 1640 cm^{-1}. M^+ 437. Yield 0.44 g (50%).

B. A mixture of 0.28 g (1 mmole) of indolylmethylenecyclohexanedione IV and 0.24 g (1.2 mmoles) of *p*-toluenesulfonyl chloride in 10 ml of pyridine was allowed to stand for 24 h at 20°C. It was then poured into ~50 ml of water and acidified with a conc. HCl. The precipitate was filtered, washed with water and 2-propanol, and compound VII was obtained in a yield of 0.25 g (56%). The melting point of a mixed sample of the compound with a sample obtained by method A did not show a depression.

2-Ethoxycarbonyl-3-amino-9-oxopyrrolo[1,2-*a*]indole (IXa, $C_{14}H_{12}N_2O_3$). A. A mixture of 25.3 g (135 mmoles) of enaminoindolinone Ia, 28.7 g (270 mmoles) of cyanoacetic ester, and 39 ml (270 mmoles) of triethylamine in 1350 ml of benzene was boiled with stirring for 5-6 h, and was then allowed to stand at 20°C for 16 h. The precipitate was filtered off, washed with benzene and methanol. Mp 249°C (dec., DMFA—methanol, 2:1). IR spectrum: 3420, 3300-3120, 1680, 1660, 1620 cm^{-1}. PMR spectrum: 1.28 (3H, t, CH_2CH_3), 4.21 (2H, q, CH_2CH_3), 7.04 (1H, s, 1-H), 7.41 (2H, br.s, NH_2), 7.26-7.91 ppm (4H, m, arom. protons). M^+ 256. Yield 25.8 g (74%).

B. A mixture of 1 g (3 mmoles) of salt Xa and 20 ml of toluene was boiled for 30 min. It was then cooled, the precipitate that separated out was filtered off and washed with methanol. Yield 0.3 g (40%). The melting point of a mixed sample of the compound with a sample obtained by method A did not show a depression.

Salt of Piperidine with Ethyl Ester of α-Cyano-β-(3-hydroxyindol-2-yl)acrylic Acid (Xa, $C_{19}H_{23}N_3O_3$). A mixture of 2.28 g (10 mmoles) of enaminoindolinone Ib, 2.1 ml (20 mmoles) of cyanoacetic ester, and 4 ml (40 mmoles) of piperidine in 110 ml of benzene was boiled with stirring for 5-6 h, and was then allowed to stand for 16 h at 20°C. The precipitate was filtered off, washed with benzene, and compound Xa was obtained in a yield of 2.7 g (87%). Mp 145-147°C (from acetonitrile). IR spectrum: 3330, 2180, 1660, 1605 cm^{-1}. M^+ 256. The melting point of a mixed sample of the compound with a sample obtained previously [3] did not show at depression.

2-Carbamoyl-3-amino-9-oxopyrrolo[1,2-*a*]indole (IXb, $C_{12}H_9N_3O_2$). A. A mixture of 3.8 g (20 mmoles) of enaminoindolinone Ia, 2.1 g (25 mmoles) of cyanoacetamide, and 3.6 ml (25 mmoles) of triethylamine in 200 ml of benzene was boiled with stirring for 6 h, and was then allowed to stand for 16 h at 20°C. Benzene was decanted. The residue was dissolved in hot methanol. The solution was cooled, the precipitate was filtered off and washed with methanol. Mp 299-300°C (from ethanol). IR spectrum: 3420, 3280, 3140, 1640, 1605, 1575 cm^{-1}. M^+ 227. PMR spectrum: 7.34 (1H, s, 1-H), 6.94-7.84 ppm (8H, m, $2NH_2$, arom. protons). Yield 0.65 g (14%).

B. A suspension of 2.27 g (7.3 mmoles) of salt Xb [3] in 75 ml of toluene was boiled with stirring for 16 h. The precipitate was filtered off and washed with methanol. Yield 0.25 g. The material was purified chromatographically on a column with silica gel using chloroform—methanol, 10:1, as eluent. R_f 0.29. Yield 0.03 g (2%). The melting point of a mixed sample of the compound with a sample obtained by method A did not show a depression.

2-Ethoxycarbonyl-3-diacetylamino-9-oxopyrrolo[1,2-*a*]indole (XIII, $C_{18}H_{16}N_2O_5$). A mixture of 4.5 g (18 mmoles) of pyrroloindole IXa and 1.44 g (18 mmoles) of fused sodium acetate in 200 ml of acetic anhydride was boiled for 7 h and was then allowed to stand for 16 h at 20°C. Sodium acetate was filtered off and acetic anhydride was evaporated to dryness. The residue was mixed with ether, the precipitate was filtered off and washed with ether. Mp 161-162°C (from methanol). IR spectrum: 1780-1680, 1610 cm^{-1}. M^+ 340. PMR spectrum (CD_3OD): 1.32 (3H, t, CH_2CH_3), 4.28 (2H, q, CH_2CH_3), 2.40 (6H, s, $N(COCH_3)_2$), 7.24 (1H, s, 1-H), 7.25-7.67 ppm (4H, m, arom. protons). Yield 5.5 g (92%).

2-Ethoxycarbonyl-3-dimethylaminomethyleneimino-9-oxopyrrolo-[1,2-*a*]indole (XIV, $C_{17}H_{17}N_3O_3$). A solution of 5.8 g (23 mmoles) of pyrroloindole IXa in 58 ml of dimethylformamide diethylacetal was boiled for 10 min. The mixture was cooled, the precipitate was filtered off and washed with the acetal and ether. Mp 167-168°C (from 2-propanol). IR spectrum: 1700, 1660, 1600 cm^{-1}. M^+ 311. PMR spectrum: 1.25 (3H, t, CH_2CH_3), 4.14 (2H q, CH_2CH_3), 3.15, 3.18 [6H, s, $(NCH_3)_2$], 7.09 (1H, s, 1-H), 7.79-7.18 (4H, m, arom. protons), 8.48 ppm (1H, s, NH). Yield 6.5 g (91%).

Benzylamide of α-Cyano-β-(3-hydroxyindol-2-yl)acrylic Acid (XIc, $C_{19}H_{15}N_3O_2$). A mixture of 1.88 g (10 mmoles) of enaminoindolinone Ia, 3.48 g (20 mmoles) of cyanoacetic acid benzylamide, and 1.5 ml (10 mmoles) of triethylamine in 100 ml of benzene was boiled with stirring for 5 h, and was then allowed to stand for 16 h at

20°C. The precipitate was filtered off, washed with benzene and methanol, mp 217-218°C (dec., from dioxane). IR spectrum: 3460, 3340, 2180, 1635, 1625 cm^{-1}. $M^{+\cdot}$ 317. PMR spectrum: 4.42 (2H, d, J ≈ 6 Hz, CH_2Ph), 7.02-7.80 (9H, m, arom. protons), 8.25 (1H, s, CH), 8.69 (1H, t, $NHCH_2Ph$), 10.69 ppm (1H, s, NH). Yield 1.65 g (52%).

Amide of α-Cyano-β-(3-hydroxyindol-2-yl)acrylic Acid (XIc, $C_{12}H_9N_3O_2$). A suspension of 1 g (3.2 mmoles) of salt Xb in 70 ml of toluene was boiled for 15 min. The mixture was cooled, the precipitate was filtered off and washed with toluene and methanol from the starting material. Mp 192-193°C (dec., from dioxane). IR spectrum: 3480, 3420, 3360, 2200, 1630, 1620 cm^{-1}. $M^{+\cdot}$ 227. PMR spectrum: 7.50 (2H, br.s, $CONH_2$), 7.01-7.78 (4H, m, arom. protons), 8.19 (1H, s, CH), 10.05 ppm (1H, s, NH). Yield 0.33 g (45%).

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