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Synthesis and Reactions of *N*-Acetyl- and *N*-(2-Chloroacetyl)-*N*-[(2*E*)-1-methylbut-2-en-1-yl]-2-iodoanilines

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Abstract—The reaction of *N*-(1-methylbut-2-en-1-yl)-2-iodaniline with Ac_2O or $ClCH_2C(O)Cl$ results in a mixture of *syn*- and *anti*-atropisomers of *N*-acetyl- and *N*-chloroacetyl-*N*-(1-methylbut-2-en-1-yl)-2-iodaniline in a ratio of 1:1. Ozonolysis of the latter followed by reduction with dimethyl sulfide in CH_2Cl_2 gives rise to the atropisomers mixture of 2-[*N*-(chloroacetyl)-*N*-(2-iodophenyl)]aminopropanal in a ratio of 1:3. When heated in boiling benzene, the mixture of atropoisomeric aldehydes reacts with triphenylphosphine to afford a mixture of 2-[(*N*-acetyl)-*N*-(2-iodophenyl)]aminopropanal atropisomers in 1:3 ratio.

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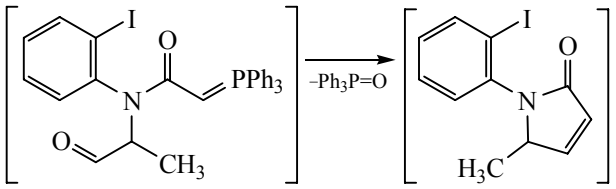
The substituted *N*-(1-methylbut-2-en-1-yl)anilines are used to obtain a wide range of *ortho*-derivatives via the aromatic Claisen aminorearrangement of the hindered indolines and substances with the pronounced anti-phytophthora activity [1]. The presence of olefin C=C bonds in these compounds make it possible to perform a number of oxidation reactions. The products of ozonation of these compounds can be reduced with borohydride to give phenylaminopropanal [2]. The *N*-allylaniline derivatives are known to be used in the construction of heterocyclic compounds via the metal-catalyzed cyclization, and most of publications in this respect are reviewed in [3].

In this work we present some results on acylation of *N*-(1-methylbut-2-en-1-yl)-2-iodoanilines, ozonation of the obtained derivatives followed by reduction to the aldehydes, and on the reaction of the resulting aldehydes with triphenylphosphine.

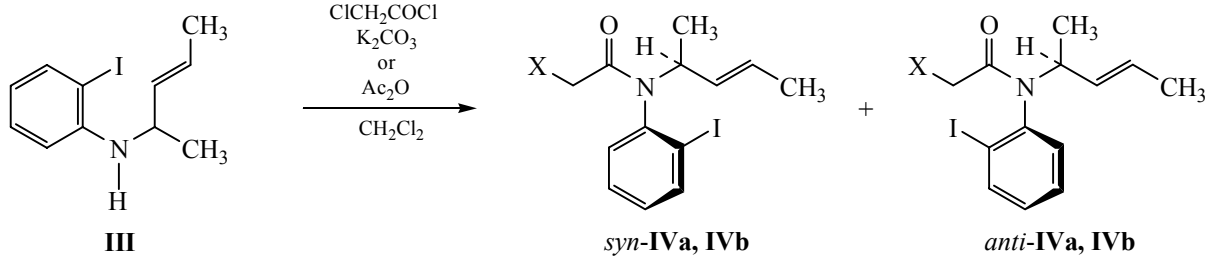
In order to obtain *N*-(1-methyl-2-oxoethyl)-*N*-(2-iodophenyl)-2-(*P*,*P*,*P*-triphenyl)phosphinydeneacetamide **I**, which could be used for the preparation of 1-(2-iodophenyl)-5-methyl-1,5-dihydrogen-2*H*-pyrrol-2-one **II** by the Wittig reaction, we synthesized the chloroacetyl derivative of *N*-(2-iodophenyl)-*N*-[(2*E*)-1-methylbut-2-en-1-yl]amine **III**.

The reaction of amine **III** with chloroacetyl chloride results in an atropisomers mixture of 2-chloro-*N*-(2-iodophenyl)-*N*-[(2*E*)-1-methylbut-2-en-1-yl]acetamide [*syn*- and *anti*-**IVa**] in a 1:1 ratio in a 85% yield. Since the subsequent studies revealed some unusual transformation, we have also obtained atropisomers of *N*-(2-iodophenyl)-*N*-[(2*E*)-1-methylbut-2-en-1-yl]acetamide (*syn*- and *anti*-**IVb**) containing acetyl group at the nitrogen atom by the reaction of amine **III** with acetic anhydride. An individualization of atropisomers *syn*-**IV** and *anti*-**IV** is not possible due to the low energy barrier to transition into each other, although they can be detected on the TLC plates due to the slightly different R_f values.



I **II**

The ^{1}H NMR spectrum of a mixture of atropisomers **IVa** and **IVb** contains a double set of the signals. The signals of methyl groups of pentenyl moiety are differentiated most clearly. The signals of the methyl group at the $C^{4'}$ carbon atom of atropisomer **IVa** are observed at 1.02 (d, *J* 7.2 Hz) and 1.35 ppm (d, *J* 6.7 Hz). The signals at 1.46 (d. d, J_1 1.0, J_2 6.5 Hz) and 1.63 ppm (d, *J* 6.2 Hz) belong to the



III *syn*-**IVa, IVb** *anti*-**IVa, IVb**

X = Cl (**a**), X = H (**b**).

protons of CH_3-group located at the $C^{2'}$ carbon atom of the double bond. The CH_2Cl-protons are magnetically non-equivalent, so in the ^1H NMR spectrum there are two groups of the well-resolved signals at 3.51 (d, J_{gem} 13.4 Hz) and 3.72 ppm (d, J_{gem} 13.4 Hz) for one, and at 3.57 (d, J_{gem} 13.5 Hz) and 3.78 ppm (d, J_{gem} 13.05 Hz) for the other atropisomer of **IVa**. Assignment to the atropisomers was done based on the geminal spin-spin coupling constants of the protons. Other proton signals of these molecules resonate in the overlapping areas.

In the ^{13}C NMR spectrum of an atropisomers **IVb** mixture, as in the case of *N*-chloroacetyl analog, the signals are also doubled. The C^2 carbon atom of the aromatic rings resonates as a singlet at 103.3 ppm. In addition, some signals of the aromatic carbon atoms are overlapped. For this reason, the ^{13}C NMR spectrum does not contain a double set of the signals for the C^3, C^4, C^5, C^6, $C^{2'}$ and $C^{3'}$ atoms.

The reduction of the ozonated atropisomers **IVa** with dimethyl sulfide results in a mixture of *syn*- and *anti*-atropisomers of 2-chloro-*N*-(2-iodophenyl)-*N*-(1-methyl-2-hydroxyethyl)acetamide **V** in a ratio of 1:3. By analogy with the known fact that in the spectrum of the *syn*-atropisomer the signal of the proton at the carbon atom bound to the nitrogen atom is in a stronger field than in the *anti*-isomer **V** [4–6], it was concluded that the *syn*-isomer of **V** (δ 4.11 ppm) is the minor one. The quartet signal at δ 4.33 ppm is assigned to the $H^{2'}$ proton of the major *anti*-isomer. There is no spin-spin coupling between this proton and the proton of the aldehyde group.

In the ^{13}C NMR spectrum of this atropisomers mixture there is a similar doubling of all the signals of the carbon atoms. The aldehyde carbon atom appears at 197.5 (*anti*-isomer) and 198.3 ppm (*syn*-isomer). The assignment is done by an explicit predominance of the first signal.

The attempts to obtain *N*-phenylpyrrole **II** from the atropisomers **V** via the reaction with triphenylphosphine in benzene, transformation into the ylides **I** of *N*-(2-iodophenyl)-*N*-[(2*E*)-1-methylbut-2-en-1-yl]acetamide phosphonium salts **VI** and subsequent Wittig olefination failed. The compound **VI** was not obtained.

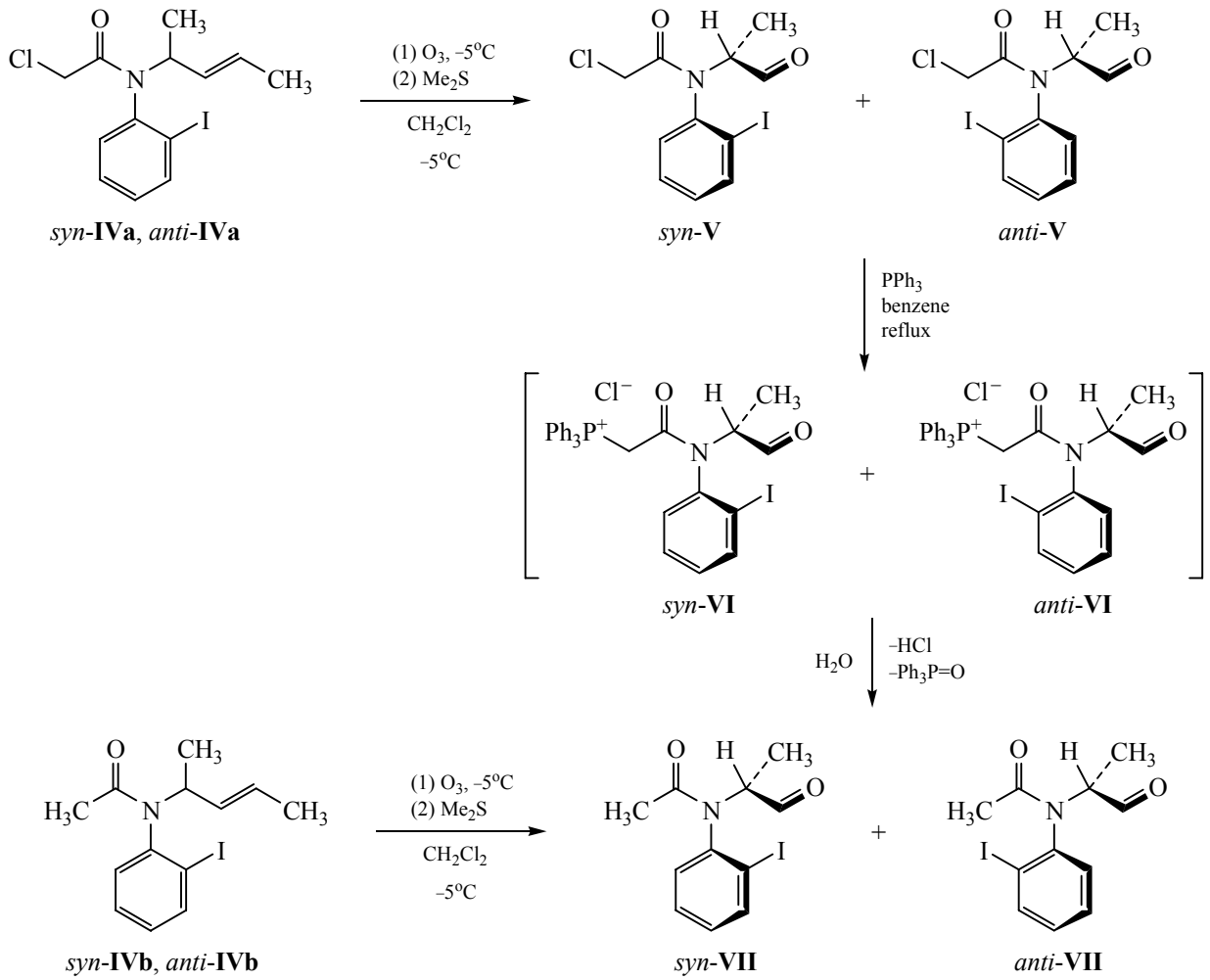
Moreover, a reduction reaction occurred where the halogen atom was replaced with a hydrogen atom. When recovering the unreacted compound **V** we isolated a significant amount of a mixture of *syn*- and *anti*-atropisomers of *N*-(2-iodophenyl)-*N*-(1-methyl-2-hydroxyethyl)acetamide **VII**. Since the heating in benzene was performed without isolation from atmospheric moisture, the water molecule may participate in this reaction. One proton of the water molecule is involved into the atropisomers formation and the other "leaves" with the chlorine anion as HCl. The oxygen atom migrates to triphenylphosphine and facilitates the separation of the latter as triphenylphosphine oxide. During the prolonged heating of the reaction mixture we registered by TLC the formation of a large amount of $Ph_3P{=}O$. The reduction of phosphonium ylide into a methyl group was observed in [7], but the occurrence of such process at the stage of the formation of quaternary triphenylphosphonium salt was not previously described.

The reduction of the ozonated atropisomers **IVb** mixture under similar conditions gives rise to a mixture of *syn*- and *anti*-atropisomers of **VII** in a ratio of 1:3 in 61% yield.

Thus, the substitution of the chlorine atom by the hydrogen atom was revealed in obtaining a quaternary phosphonium salt from PPh_3 and 2-chloro-*N*-(2-iodophenyl)-*N*-(1-methyl-2-hydroxyethyl)acetamide.

EXPERIMENTAL

The IR spectra were recorded on a FT-IR Prestige-21 Shimadzu spectrophotometer. The ^1H and ^{13}C NMR spectra were taken on a Bruker AM 300 (300.13 and 75.45 MHz) and Bruker Avance III 500 (500.13 and 125.73 MHz) instruments with respect to internal



syn-**IVa**, *anti*-**IVa** *syn*-**V** *anti*-**V**

syn-**VI** *anti*-**VI**

syn-**IVb**, *anti*-**IVb** *syn*-**VII** *anti*-**VII**

X = Cl (**a**), X = H (**b**).

TMS. The elemental analysis was performed on a CHN Analyzer M-185B. The purity of the samples was determined on a Chromos GC-1000 complex using helium as a carrier gas, flame-ionization detector, column 1 m × 3 mm, 5% SE 30 on a Chromaton N-AW carrier. TLC analysis was performed using Sorbfil plates (Sorbpolimer, Krasnodar) and detecting with UV irradiation (λ 254 nm) or in iodine vapor.

***N*-(2-Iodophenyl)-*N*-[(2*E*)-1-methylbut-2-en-1-yl]amine (III).** To a solution of 20.5 g (94 mmol) of 2-iodoaniline in 50 ml of triethylamine were added 15 g of chloropentene. The reaction mixture was boiled for 10 h. The triethylamine excess was removed on a rotary evaporator. To the residue was added a solution of 20 g of NaOH in 100 ml of H_2O. The organic layer was separated, dried with KOH, concentrated. and distilled in a vacuum. Yield 24 g (89%), bp 135–140°C (2 mm Hg). ^{1}H ($CDCl_3$), δ, ppm: 1.30 d (3H, CH_3, *J* 6.7 Hz), 1.55 d (3H, CH_3, *J* 6.2 Hz), 3.85 m (1H, $H^{4'}$), 4.05 br. s (1H, NH), 5.35 d. d (1H, H^3, *J* 4.4, 15.5 Hz), 5.55 d. q (1H, H^2, *J* 6.2, 15.5 Hz), 6.35 d. d (1H, ArH, *J* 7.2, 7.8 Hz), 6.52 d (1H, ArH, *J* 8.3 Hz), 7.05 d. d (1H, ArH, *J* 7.2, 8.3 Hz), 7.55 d (1H, ArH, *J* 7.8 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 16.9, 17.7, 17.9, 19.8 (CH_3); 43.5, 43.6 (CH_2Cl); 54.2, 56.5 ($C^{4'}$), 103.3 (C^2); 127.8, 128.3, 128.6, 129.5, 130.4, 130.7, 130.9, 131.1, 140.4 (C^3, C^4, C^5, C^6, $C^{2'}$, $C^{3'}$), 141.0, 141.6 (C^1), 165.2, 165.5 (N–C=O). Found, %: C 45.90; H 4.88; I 44.07; N 4.82. $C_{11}H_{14}IN$. Calculated, %: C 46.01; H 4.91; I 44.20; N 4.88.

2-Chloro-*N*-(2-iodophenyl)-*N*-[(2*E*)-1-methylbut-2-en-1-yl]acetamide (IVa) (atropisomers mixture)**.** To a solution of 5.94 g (20 mmol) of amine **III** in 30 ml of anhydrous CH_2Cl_2 was added 2.5 g of chloroacetyl chloride (1.8 ml) in 5 ml of CH_2Cl_2 and 2.76 g

(40 mmol) of K_2CO_3 under stirring. The reaction progress was monitored by TLC (C_6H_6–EtOAc, 95:5). After the disappearance of the starting amine, to the reaction mixture was added H_2O, the product was extracted with CH_2Cl_2 (100 ml). The organic layer was washed with water, dried over Na_2SO_4. The solvent was evaporated, and the residue was chromatographed on a silica gel eluting with benzene. Yield 6.2 g (85%), R_f 0.5 (C_6H_6). ^{1}H ($CDCl_3$), δ, ppm: 1.02 d (3H, CH_3, *J* 7.2 Hz), 1.35 d (3H, CH_3, *J* 6.7 Hz), 1.47 d. d (3H, CH_3, J_1 1.0, J_2 6.5 Hz), 1.64 d (3H, CH_3, *J* 6.2 Hz); 3.51 d, 3.55 d, 3.71 d, 3.79 d (2H, CH_2Cl, J_{gem} 13.2 Hz), 4.85–5.69 m (3H, $H^{4'}$, $H^{2'}C{=}CH^{3'}$), 7.03 t. t (ArH, J_1 1.5, J_2 7.5 Hz), 7.20 d. t (ArH, J_1 1.5, J_2 7.5 Hz), 7.32–7.39 m (1H, ArH), 7.84–7.90 m (ArH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 16.9, 17.7, 17.9, 19.8 (CH_3), 43.5, 43.6 (CH_2Cl); 54.2, 56.5 ($C^{4'}$), 103.3 (C^2); 127.8, 128.6, 129.5, 130.4, 130.7, 130.9, 131.1, 140.4 (C^3, C^4, C^5, C^6, $C^{2'}$, $C^{3'}$); 141.0, 141.6 (C^1), 165.2, 165.5 (N–C=O). Found, %: C 42.82; H 4.11; Cl 9.68; I 34.78; N 3.80. $C_{13}H_{15}ClINO$. Calculated, %: C 42.94; H 4.16; Cl 9.75; I 34.90; N 3.85.

***N*-(2-Iodophenyl)-*N*-[(2*E*)-1-methylbut-2-en-1-yl]-acetylamide (IVb)** (atropisomers mixture)**.** To a solution of 1.59 g (5.78 mmol) of amine **III** in 30 ml of anhydrous CH_2Cl_2 was added 1 ml (12 mmol) of Ac_2O. After 24 h, the reaction mixture was diluted with H_2O (20 ml) and then extracted with $CHCl_3$ (100 ml). The organic layer was washed with water and dried over Na_2SO_4. The solvent was evaporated, and the residue was chromatographed on a silica gel eluting with benzene. Yield 0.97 g (55%), R_f 0.5 (C_6H_6). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.09 d (3H, CH_3, *J* 7.1 Hz), 1.40 d (3H, CH_3, *J* 6.5 Hz), 1.55 d (3H, CH_3, *J* 6.4 Hz), 1.72 d (3H, CH_3, *J* 5.9 Hz), 1.78 s (3H, CH_3), 1.82 s (3H, CH_3), 5.05 quintet (1H, CH, *J* 7.1 Hz), 5.19–5.33 m (2H, CH, HC=C), 5.54–5.67 m (3H, HC=CH, C=CH), 7.07 t (ArH, *J* 7.5 Hz), 7.22 d (ArH, *J* 7.7 Hz), 7.36–7.45 m (ArH), 7.92–7.99 m (ArH). Found, %: C 47.31; H 4.85; I 38.41; N 4.18. $C_{13}H_{15}ClINO$. Calculated, %: C 47.43; H 4.90; I 38.55; N 4.26.

2-Chloro-*N*-(2-iodophenyl)-*N*-(-1-methyl-2-oxoethyl)acetamide (V) (atropisomers mixture)**.** Through a solution of 3.63 g (10 mmol) of the atropisomers **IVa** mixture in 40 ml of CH_2Cl_2 was passed an ozone-oxygen mixture for 11.1 min (54 mmol h^{-1}) at –5°C. Then the reaction mixture was purged with argon for 1 min. After 20 min, to the reaction mixture was added 2 ml of dimethyl sulfide, and the reaction mixture was kept for 2 h. Then the solvent was evaporated, and the residue was chromatographed on a silica gel eluting with a C_6H_6–EtOAc mixture (10:1). Yield 1.9 g (54%), viscous substance, R_f 0.3 (C_6H_6:EtOAc = 19:1). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.55 d (3H, CH_3, *J* 7.3 Hz), 3.77 d (1H, $H^{2''A}$, J_{gem} 13.7 Hz), 3.78 d (1H, minor, $H^{2''A}$, *J* 13.5 Hz), 3.87 d (1H, $H^{2''B}$, *J* 13.7 Hz), 3.92 d (1H, minor, $H^{2''B}$, *J* 13.5 Hz), 4.11 q (1H, minor, H^2, *J* 7.3 Hz), 4.33 q (1H, H^2, *J* 7.3 Hz), 7.15–7.55 m (ArH), 7.97–8.03 m (ArH), 9.82 s (1H, minor, CHO), 9.87 s (1H, CHO). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 11.2, 13.6 (CH_3); 42.1, 42.4 (CH_2Cl); 63.2, 65.2 (C^2); 101.0, 101.1 ($C^{2'}$); 128.1, 130.1, 130.3, 130.4, 130.6, 130.8, 131.0, 140.4 ($C^{3'}$, $C^{4'}$, $C^{5'}$, $C^{6'}$), 140.6, 141.1 ($C^{1'}$); 166.2, 166.3 (N–C=O); 197.5, 198.3 (CHO). Found, %: C 37.47; H 3.11; Cl 10.01; I 36.00; N 3.93. $C_{11}H_{11}ClINO_2$. Calculated, %: C 37.58; H 3.15; Cl 10.08; I 36.10; N 3.98.

***N*-(2-Iodophenyl)-*N*-(-1-methyl-2-oxoethyl)acetamide (VII)** (atropisomers mixture, 1:3)**.** *a*. A solution of 1.41 g (4 mmol) of amide **V** and 1.05 g (4 mmol) of PPh_3 in 8 ml of toluene was refluxed for 39 h. Then the solvent was evaporated, and the residue was chromatographed on a silica gel eluting with a C_6H_6–EtOAc mixture (10:1). 0.6 g (43%) of the starting amide **V** was recovered. Yield 0.31 g (24%).

b. Compound **VII** was obtained similarly to amide **V** via the ozonation and subsequent reduction with dimethylsulfide, 3.29 g (13 mmol) of atropisomers mixture **IVb** in CH_2Cl_2. Yield 1.9 g (61%), amorphous powder, R_f 0.2 (C_6H_6:EtOAc=19:1). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.40 d (3H, CH_3, *J* 7.2 Hz), 1.77 s (3H, CH_3), 1.82 s (3H, CH_3), 3.99 q (1H, minor, H^2, *J* 7.4 Hz), 4.07 q (1H, H^2, *J* 7.4 Hz), 7.05–7.35 m (ArH), 7.40 d (1H, *syn*-, ArH, *J* 8.0 Hz), 7.83 d (1H, *anti*-, ArH, *J* 8.0 Hz), 9.75 s (1H, *syn*-, CHO), 9.80 s (1H, *anti*-, CHO). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 11.6, 14.0 (CH_3); 22.6, 22.8 (CH_3); 62.9, 64.4 (C^2); 101.3, 101.5 (C–I); 128.8, 129.2, 130.0, 130.1, 130.3, 130.4, 138.8, 140.4 ($C^{3'}$, $C^{4'}$, $C^{5'}$, $C^{6'}$); 143.2, 144.4 ($C^{1'}$); 170.6, 170.9 (N–C=O); 198.3, 199.2 (CHO). Found, %: C 41.56; H 3.75; I 39.87; N 4.35. $C_{11}H_{12}INO_2$. Calculated, %: C 41.66; H 3.81; I 40.02; N 4.42.

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