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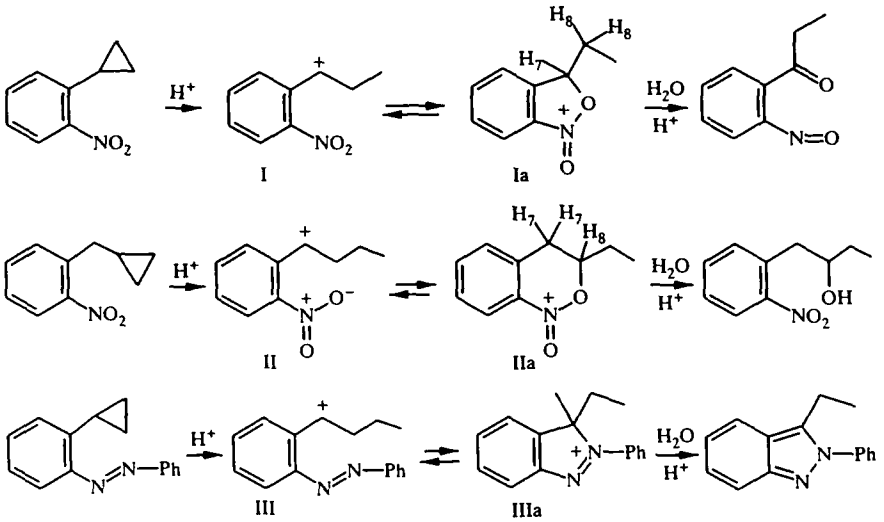
# 2-CYCLOPROPYLBENZOIC ACIDS IN THE SYNTHESIS OF PHTHALIDES AND 3,4-DIHYDROISOCOUMARINS

**S. S. Mochalov, A. N. Fedotov, T. G. Kutateladze, E. V. Trofimova, Yu. S. Shabarov, and N. S. Zefirov**

*2-Cyclopropylbenzoic acids, under the action of strong protic acids ($FSO_3H$, $H_2SO_4$), are converted to 3-ethylphthalidium ions. In solutions in these inorganic acids, the 3-ethylphthalidium ions are isomerized to 3-methyl-3,4-dihydroisocoumarinium ions. As a result, a thermodynamic equilibrium is established, with the concentrations of both types of cyclic ions depending on the nature of the substituent in the aromatic part of the substrate. Neutralization of the original solutions of 3-ethylphthalidium ions or a mixture of these with 3-methyl-3,4-dihydroisocoumarinium ions, gave either 3-ethylphthalides or their mixtures with 3-methyl-3,4-dihydroisocoumarins. The neutral 3-ethylphthalides and 3-methyl-3,4-dihydroisocoumarins, when subjected to the action of inorganic acids, are also isomerized to form in each case a mixture of ions with concentrations matching the concentrations of ions formed from the corresponding 2-cyclopropylbenzoic acids.*

The nitro group, its isoelectronic analog the azoxy group, and also the azo group, when they are spatially close to the three-carbon ring in the corresponding substituted phenylcyclopropanes or benzylcyclopropanes, may manifest the properties of internal nucleophiles and thus effectively stabilize the carbenium ions that are formed upon cleavage of the cyclopropane ring in these substrates under the influence of strong protic acids [1-8]. As a result of such intramolecular stabilization, stable heterocyclic ions of the type of Ia-IIIa are formed (see Scheme 1), intermediates that determine the direction of conversion of the original cyclopropyl-substituted nitro-, azoxy-, or azobenzenes to neutral products of acid-catalyzed reactions.

Scheme 1




This process of intramolecular stabilization of the corresponding carbenium ions of the type of I-III (Scheme 1) is dynamic in nature; and the heterocyclic ions that are formed in the kinetically controlled stage of the reaction are capable, in

M. V. Lomonosov Moscow State University, Moscow 119899, Russia. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 321-326, March, 1998. Original article submitted June 27, 1997.

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TABLE 1. Contents of Ions VIa-c and Xa-c Formed from 2-Cyclopropylbenzoic Acids IVa-c in Fluosulfonic Acid in the Kinetically Controlled Stage of the Reaction, and under Conditions of Thermodynamic Equilibrium

| Original acid | Ratio of ions VIa-c to Xa-c, %* | |
|---|---|---|
| | reaction time 15 min | reaction time 2 months** |
| IV.a | 100 : 0 | 58 : 42 |
| IV b | 100 : 0 | 46 : 54 |
| IV c | 100 : 0 | 61 : 39 |

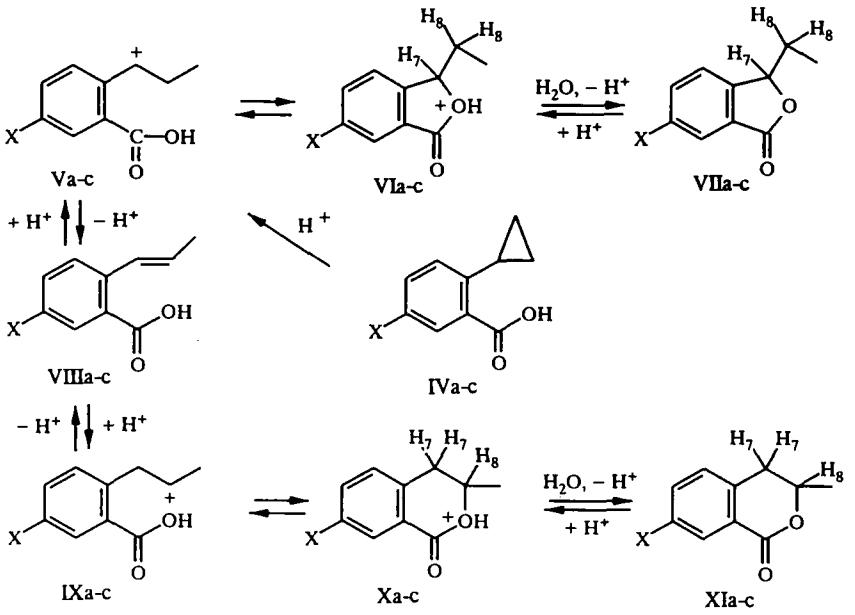
*According to $^1H$ NMR spectra.

**After this time, the ratio of ions did not change.

the course of time, of reversible isomerization to heterocyclic ions of a different structure. As a result, a thermodynamic equilibrium is established, with the concentrations of the isomeric cyclic ions depending on the nature of the substituent on the aromatic ring in the para position relative to the carbenium center that is formed [4, 9-11].

In further development of the intramolecular conversions of ortho-substituted arylcyclopropanes that we had found previously, in the present work we investigated the acid-catalyzed reactions of 2-cyclopropylbenzoic acids. We found that the carboxy group in 2-cyclopropylbenzoic acids IVa-c, the same as in the previously indicated groupings (Scheme 1), is capable of participating in intramolecular stabilization of the carbenium ions that are formed upon cleavage of the cyclopropyl ring of substrates under the influence of fluosulfonic acid or concentrated sulfuric acid. In this case, immediately after mixing the reagents, cyclic ions with a five-membered structure are formed exclusively; these are the protonated 3-ethylphthalides VIa-c (Scheme 2).

Scheme 2




IV–XI a) X = H, b) X = Br, c) X = Et

We found that the 3-ethylphthalidium ions VIa-c are so stable in the solutions of these inorganic acids at 20°C that they did not change appreciably during the course of 24 h, as monitored by $^1H$ NMR. However, with longer periods of contact with the acids ($FSO_3H$, $H_2SO_4$), the cyclic ions VIa-c are gradually isomerized to ions with a six-membered structure Xa-c; and, in approximately 2 months, a thermodynamic equilibrium is established in which the ratio of concentrations of the two types of ions was found to dependent on the nature of the substituent on the benzene ring in the para position relative to the alkyl chain in which the carbenium ion center is generated (see Table 1).

TABLE 2. Parameters of IR and $^1H$ NMR Spectra of Synthesized Compounds

| Compound | Chemical shifts δ, ppm | | | | | ν, $cm^{-1}$ |
|---|---|---|---|---|---|---|
| | 7-H | 8-H | $CH_3$ | $C_2H_5$ | aromatic protons | |
| VIa | 6,36 d. d, (1H) | 2,26 m (2H) | 1,11 t (3H) | – | 7,60...8,32 m (4H) | – |
| VIb | 6,35 d. d, (1H) | 2,17 m (2H) | 1,06 t (3H) | – | 7,66 (1H, d, 3-H); 8,28 (1H, d. d, $J_{43}$ = 8Hz, 4-H); 8,37 (1H, d, $J_{65}$ = 1,5 Гц, 6-H) | – |
| VIc | 6,28 d. d, (1H) | 2,12 m (2H) | 1,03 t (3H) | 1,26 t (3H); 2,75 q (2H) | 7,32...8,07 m (3H) | – |
| Ia* | 6,82 d. d, (1H) | 2,48 m (2H) | 1,27 t (3H) | – | 8,08 (1H, t, $J_{45}$ = 8,0Hz, $J_{43}$ = 8,5Hz, 4-H); 8,10 (1H, d, $J_{65}$ = 8,0Hz, 6-H); 8,40 (1H, d, $J_{34}$ = 8,5Hz, 3-H); 8,47 (1H, t, $J_{54}$ = $J_{56}$ = 8,0Hz) | – |
| VIIa | 5,50 d. d, 1H) | 1,93 m (2H) | 0,93 t (3H) | – | 7,43...7,88 m (4H) | 1760 (C=O) |
| VIIb | 5,30 d. d, (1H) | 1,92 m (2H) | 0,96 t (3H) | – | 7,28 (Hz, d., $J_{34}$ = 9Hz, 3-H); 7,69 (1H, d. d, $J_{43}$ = 9Hz, $J_{46}$ = 2Hz, 4-H); 7,90 (1H, d, $J_{64}$ = 2Hz, 6-H) | 1780 (C=O) |
| VIIc | 5,29 d.d, (1H) | 1,91 m (2H) | 0,93 t (3H) | 1,22 t (3H); 2,65 q (2H) | 7,08...7,66 m (3H) | 1780 (C=O) |
| Xa | 3,38 d (2H) | 5,50 m (1H) | 1,76 d (3H) | – | 7,60...8,32 m (4H) | – |
| Xb | 3,24 d (2H) | 5,48 m (1H) | 1,70 d (3H) | – | 7,42 (1H, d, $J_{64}$ = 2Hz, 6-H); 8,09 (1H, d. d, $J_{43}$ = 8Hz, $J_{46}$ = 2Hz, 4-H); 8,36 (1H, d, $J_{34}$ = 8Hz, 3-H) | – |
| IIa'** | 3,68 m (2H) | 6,06 m (1H) | 1,93 d (3H) | – | 7,73 (1H, d, $J_{34}$ = 8,5Hz, 3-H); 7,79 (1H, t, $J_{43}$ = 8,5Hz, $J_{45}$ = 8Hz, 4-H); 8,23 (1H, t, $J_{54}$ = 8Hz, $J_{56}$ = 8Hz, 5-H); 8,28 (1H, d, $J_{65}$ = 8Hz, 6-H) | – |
| XIa | 2,83 d (2H) | 4,52 m (1H) | 1,45 d (3H) | – | 7,01...8,08 m (4H) | 1730 (C=O) |
| XIb | 2,95 d (2H) | 4,72 м (1H) | 1,54 d (3H) | – | 7,23 (1H, d, $J_{65}$ = 8Hz, 6-H); 7,75 (1H, d. d, $J_{56}$ = 8Hz, $J_{53}$ = 2,5Hz, 5-H); 8,33 (1H, d, $J_{35}$ = 2,5Hz, 3-H) | 1725 (C=O) |
| XIc | 2,82 d (2H) | 4,65 м (1H) | 1,47 d (3H) | 1,24 t (3H); 2,68 q (2H) | 6,80...7,86 m (3H) | 1725 (C=O) |

*Data from [12].

**Ion IIa' is isomeric with ion Ia and has a structure analogous to that of ion IIa (see Scheme 1); chemical shifts for ion IIa' are taken from [12].

We had also observed a similar dependence of the equilibrium concentrations of ions on the nature of the substituent on the benzene ring of the substrate in the case of N-oxo-3-ethylbenz[2,1]isoxazolinium and N-oxo-3-methylbenz[2,1]oxazinium ions, which have structures similar to those of the ions VIa-c and Xa-c, and which are formed from 4-substituted 2-nitrophenylcyclopropanes under the influence of fluosulfonic acid [4]. The only distinctive feature in the comparison of equilibrium concentrations of five and six-membered cyclic ions is that a longer time (~3 months) is required to reach the equilibrium state in the case of the substituted 2-nitrophenylcyclopropanes [4], in comparison with the corresponding 2-cyclopropylbenzoic acids (see above).

Ice-water treatment of sulfuric acid solutions of the 3-ethylphthalidium salts VIa-c that are formed immediately after dissolving 2-cyclopropylbenzoic acids in concentrated sulfuric acid, affords exclusively the 3-ethylphthalides VIIa-c, whereas the same sort of treatment of sulfuric acid solutions of those same acids IVa-c that had been held for 2 months at 20°C affords two neutral reaction products in each case, a 3-ethylphthalide and a 3-methyl-3,4-dihydroisocoumarin, in a ratio corresponding to the equilibrium concentration of the corresponding cyclic ions (see Table 1 and Experimental section).

The structures of the cyclic ions VIa-c and Xa-c and the neutral phthalides VIIa-c and 3-methyl-3,4-dihydroxyisocoumarins XIa-c that are formed from these cyclic ions were confirmed by $^1H$ NMR, $^{13}C$ NMR, and IR spectroscopy, and also by mass spectrometry (see Table 2).

In the $^1H$ NMR spectra, the chemical shifts of the signals from the protons of the aliphatic part of the ions formed immediately after mixing the 2-cyclopropylbenzoic acids with fluosulfonic acid are found to correlate with the corresponding chemical shifts of the signals from the protons of the five-membered cyclic ions that are obtained from 2-nitrophenylcyclopropanes under the same conditions (see compound Ia in Scheme 1 and Table 2), thus providing a direct indication of the identity of the heterocyclic cores of the ions formed under the conditions of reaction in both cases. Here, exactly the same correlation in the $^1H$ NMR spectra is observed in the case of the six-membered cyclic ions formed both from the 2-cyclopropylbenzoic acids and from the 2-nitrophenylcyclopropanes (see Table 2).

With regard to the mechanism of the isomeric interconversion of the cyclic ions VIa-c and Xa-c, it is most probably accomplished through stages of deprotonation of the corresponding open forms of the ions Va-c and IXa-c (see Scheme 2) and protonation of the intermediate that is common for each pair of cyclic ions, the corresponding 2-cyclopropenylbenzoic acids VIIIa-c. The proposed isomerization scheme (which does not go through a hydride shift in the open-structure ions) is consistent with the results from a special study of isomeric conversions of cyclic ions formed from 2-nitrophenylcyclopropanes under the action of $D_2SO_4$ [13].

Next we were able to establish that the 3-ethylphthalides VIIa-c and 3-methyl-3,4-dihydroisocoumarins XIa-c, when isolated in individual form and dissolved separately in fluosulfonic acid (or $H_2SO_4$), are protonated at the ether oxygen atom, being converted to ions with exactly the same structure as that of the ions formed directly in these acids from the 2-cyclopropyl-substituted benzoic acids IVa-c. This is indicated by the identity of $^1H$ NMR spectra of solutions of the ions obtained by dissolution in fluosulfonic acid in one case of the substrates IVa-c, and in the other case by dissolution of the neutral products of rearrangement of these substrates (compounds VIIa-c and XIa-c). Here, the same as in the case of cyclic ions formed directly from 2-cyclopropylbenzoic acids IVa-c, the individual ions obtained by protonation of the 3-ethylphthalides VIIa-c or the 3-methyl-3,4-dihydroisocoumarins XIa-c also undergo isomeric conversions so that after the necessary interval of time (~2 months), thermodynamic equilibrium is established in each case, with exactly the same concentration ratio of five- and six-membered cyclic ions as is characteristic for the equilibrium state of the analogous ions formed directly from the acids IVa-c (see Table 1).

Thus, the acid-catalyzed rearrangement of 2-cyclopropylbenzoic acids that we have found, along with the relationships in the isomeric conversions of the cyclic ions formed on the path of the reaction, will open up broad possibilities in the synthesis of difficulty accessible functional derivatives of phthalides and 3-methyl-3,4-dihydroisocoumarins.

## EXPERIMENTAL

The $^1H$ NMR spectra were registered in a Tesla-BS 467 instrument with a working frequency of 60 MHz and in Varian-XL 100 and Bruker-AM 250 instruments, internal standard TMS or $CHCl_3$ for solutions of the fluosulfonates in $FSO_3H$, solvents $CCl_4$, $CDCl_3$, $H_2SO_4$, $FSO_3H$. The $^{13}C$ NMR spectra were obtained in a Varian-FT 80A instrument, working frequency 20 MHz, under conditions of complete and incomplete coupling from protons, solvents $CDCl_3$, $FSO_3H$, $D_2SO_4$. The IR spectra were taken in a film or in white mineral oil on a UR-20 instrument. The mass spectra were obtained in a

Varian-MAT 44S quadrupole mass spectrometer and in a Varian-MAT 212 sector magnetic instrument, using a system for direct introduction of the sample into the ion source; electron energy 70 eV. The purities of the original compounds were monitored on Silufol plates. Preparative separation of the mixtures was accomplished on 40/100μ silica gel, eluent ether–pentane.

**2-Cyclopropylbenzoic acids (IVa-c)** were synthesized by hydrolysis of the corresponding amides of 2-cyclopropylbenzoic acids. **Standard procedure:** To 200 ml of a 25% NaOH solution and 100 ml of methyl alcohol, 0.042 mole of the 2-cyclopropylbenzamide was added in portions. The reaction mixture was refluxed with stirring for 24 h and then cooled and acidified with 200 ml of concentrated HCl; the precipitated crystals were filtered off, washed with ice water, and recrystallized from alcohol.

Using this procedure, from 6.76 g of 2-cyclopropylbenzamide, we obtained 4.6 g (70%) of **2-cyclopropylbenzoic acid (IVa)**, mp 105°C [14]; from 10.08 g of 5-bromo-2-cyclopropylbenzamide, we obtained 9.2 g (91%) of **5-bromo-2-cyclopropylbenzoic acid (IVb)**, mp 126-127°C. PMR spectra: 0.3-1.16 (4H, m, cyclopropane) and 2.45-2.95 (1H, m, cyclopropane), 6.84 (1H, d, $J_{34}$ = 9 Hz, 3-H); 7.50 (1H, d.d, $J_{43}$ = 9.0 Hz, 4-H); 8.10 (1H, d, $J_{64}$ = 2.0 Hz, 6-H); 12.5 md (1H, br.s, COOH). IR spectrum: 1700 (C=O), 2400...2800 $cm^{-1}$ (OH). Found, %: C 49.50; H 3.65; Br 33.0. $C_{10}H_9BrO_2$. Calculated, %: C 49.82; H 3.76; Br 33.15. From 7.95 g of 2-cyclopropyl-5-ethylbenzamide, we obtained 3.83 g (48%) of **2-cyclopropyl-5-ethylbenzoic acid (IVa)**, mp 72-73°C. PMR spectrum: 0.87-1.5 (7H, m, cyclopropane and $\underline{CH_3}CH_2$); 1.72-2.25 (1H, m, cyclopropane); 2.70 (2H, q, $CH_3\underline{CH_2}$); 7.13-8.23 (3H, m, ArH); 11.01 ppm (1H, br.s, COOH). IR spectrum: 1700 (C=O), 2400-3000 $cm^{-1}$ (OH). Found, %: C 75.83; H 7.43. $C_{12}H_{14}O_2$. Calculated, %: C 75.76; H 7.42.

**Preparation of Solutions of Ions VIa-c or Their Mixtures with Ions Xa-c in Fluosulfonic Acid for Registration of $^1H$ NMR and $^{13}C$ NMR Spectra (standard procedure).** To 0.5 ml of $FSO_3H$, chilled to −30°C, 0.18 mmole of the appropriate 2-cyclopropylbenzoic acid IVa-c was added in portions. After dissolution of the substrate, the reaction mixture was warmed to room temperature and placed in an ampul for taking the spectra, after which the $^1H$ and $^{13}C$ NMR spectra were recorded immediately. The solutions were held in the ampuls for 1.5-3 months with periodic recordings of the spectral characteristics ($^1H$ NMR spectra of ions VIa-c and Xa-c are given in Table 2). The $^{13}C$ NMR spectrum of the 3-ethylphthalidium (VIa) is as follows: 7.63; 25.67; 97.82; 119.94; 122.56; 127.31; 131.10; 140.39; 153.25; 183.19 ppm; that of 3-methyl-3,4-dihydroisocoumarinium (Xa) is 17.83; 32.00; 88.39; 128.60; 128.82; 131.09; 131.57; 140.73; 141.44; 179.10 ppm.

**Rearrangement of 2-Cyclopropylbenzoic Acids (IVa-c) under the Action of Concentrated Sulfuric Acid (standard procedure).** To 15 ml of concentrated $H_2SO_4$, chilled to −20°C, 0.01 mole of the appropriate 2-cyclopropylbenzoic acid was added in portions while stirring. The reaction mixture was held for 1 h at −15° to −5°C, poured into 100 ml of ice water, and neutralized with sodium carbonate solution. The organic compounds were extracted with ether (or chloroform), washed with water, and dried with $MgSO_4$. After evaporating the solvent, the residue was chromatographed on silica gel with ether–hexane eluent.

Using the standard procedure, from 3.2 g (0.02 mole) of 2-cyclopropylbenzoic acid (IVa), we obtained 3.05 g (95%) of **3-ethylphthalide (VIIa)**, mp 121-122°C (3 mm Hg), $n_D^{20}$ 1.5718 [15]. Analogously, from 2.41 g (0.01 mole) of 5-bromo-2-cyclopropylbenzoic acid (IVb), we obtained 2.24 g (93%) of **6-bromo-3-ethylphthalide (VIIb)**, mp 49-50°C. Mass spectrum, m/z (and $I_{rel}$, %): $M^+$ 240 (11), 183 [M $-C_2H_5CO$] (20). Found, %: C 49.63; H 3.70. $C_{10}H_9BrO_2$. Calculated, %: C 49.82; H 3.76. Similarly, from 1.9 g (0.01 mole) of 5-ethyl-2-cyclopropylbenzoic acid (IVc), we obtained 1.56 g (82%) of **3,6-diethylphthalide (VIIc)**. Viscous oil. Mass spectrum, m/z (and $I_{rel}$, %): $M^+$ 190 (29), 161 [M-$C_2H_5$] (100), 133 (M $-C_2H_5CO$] (54). Found, %: C 75.63; H 7.25. $C_{12}H_{14}O_2$. Calculated, %: C 75.76; H 7.42.

**Isomerization of Cyclic Ions VIa-c to Ions Xa-c and Segregation of Neutral Compounds VIIa-c and XIa-c (standard procedure).** A sulfuric acid solution of the appropriate 2-cyclopropylbenzoic acid IVa-c, obtained by the above-described method, was held at 20-22°C for two months, after which it was poured into ice water with stirring, and the reaction products were extracted and separated as indicated above. From 1.62 g (0.01 mole) of compound IVa, we obtained 0.91 g (56%) of **3-ethylphthalide (VIIa)** and 0.66 g (41%) of **3-methyl-3,4-dihydroisocoumarin (XIa)**, mp 53°C. $^{13}C$ NMR spectrum: 20.91; 34.90; 75.06; 127.31; 127.62; 128.27; 130.26; 133.66; 139.09; 184.95 ppm. Mass spectrum, m/z (and $I_{rel}$, %): $M^+$ 162 (12), 118 [M-$CH_3CHO$] (39).

Analogously, from 1.2 g (0.005 mole) of compound IVb, we obtained 0.48 g (40%) of **6-bromo-3-ethylphthalide (VIIb)** and 0.59 g (49%) of **5-bromo-3-methyl-3,4-dihydroisocoumarin** (XIb), mp 121-122°C. Mass spectrum, m/z (and $I_{rel}$, %): $M^+$ 240, 242 (39), 196, 198 [M − $CH_3CHO$] (100), 168, 170 [M − $CH_3CHO$ − CO] (46).

Similarly, from 1.9 g (0.01 mole) of compound IVc, we obtained 0.86 g (45%) of **3,6-diethylphthalide (VIIc)** and 0.53 g (28%) of **3-methyl-7-ethyl-3,4-dihydroisocoumarin (XIc).** Viscous oil. Found, %: C 75.54; H 7.31. $C_{12}H_{14}O_2$. Calculated, %: C 75.76; H 7.42.

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