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2-Acyl(aroyl)-1,1,3,3-tetracyanopropenides: IV.* Synthesis of 1-alkyl(aryl)-4-amino-6-iodo-3-oxo-1,3-dihydrofuro[3,4-*c*]pyridine-7-carbonitriles

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Abstract—The reaction of sodium 2-acyl(aroyl)-1,1,3,3-tetracyanopropenides with hydroiodic acid at heating led to the formation of 1-alkyl(aryl)-4-amino-6-iodo-3-oxo-1,3-dihydrofuro[3,4-c]pyridine-7-carbonitriles.

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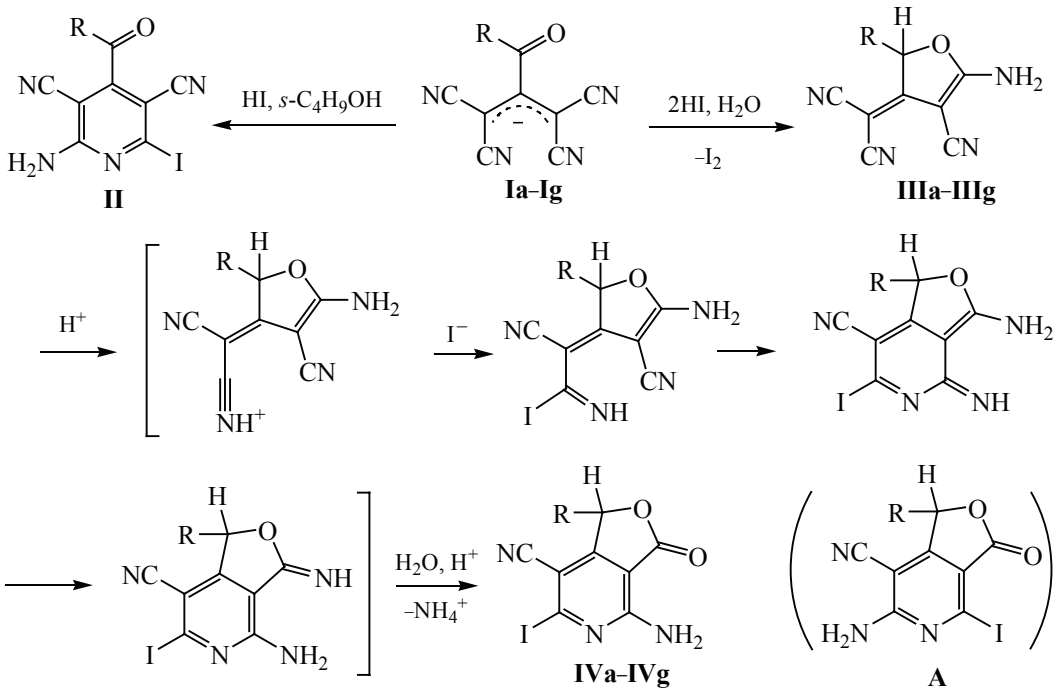
2-Acyl(aroyl)-1,1,3,3-tetracyanopropenides **Ia–Ig** are promising initial compounds for the synthesis of various heterocyclic compounds [1–5]. It was shown [1] that the reaction of propenides **I** with HI depending on the applied solvent made it possible to obtain derivatives either of pyridine **II** or of dihydrofurane **III**. In both cases the reaction products are capable of further heterocyclization providing fused systems including furan and pyridine rings. The polyfunctional compounds based on the furo[3,4-*c*]pyridine system are of interest as potential pharmaceuticals since many among them exhibit diverse physiological action [6–11].

The research showed that 2-iodopyridines **II** did not react with hydrogen halides, but dihydrofuranes **III** at heating to boiling with hydroiodic acid underwent fast transformation into 1-alkyl(aryl)-4-amino-6-iodo-3-oxo-1,3-dihydrofuro[3,4-*c*]pyridine-7-carbonitriles **IV**. Since the dihydrofurans **III** formed by the reaction of propenides **I** with HI in water solution we investigated the possibility to synthesize furo[3,4-*c*]pyridines **IV** by a direct reaction proceeding from propenides **I**. To this end we studied the effect of the reaction conditions (temperature, duration, HI concentration) in the system propenide **Ia–Ig**–HI. The best results were obtained at a short (1–3 min) boiling of propenides **Ia–Ig** with concn. HI. As a result furo[3,4-*c*]pyridines **IVa–IVg** were obtained in 58–84% yields.

The structure of compounds **IVa–IVg** was derived from the analysis of ^{1}H NMR and mass spectra and was consistent with the data of IR spectroscopy and elemental analysis. In the ^{1}H NMR spectra the amino group at the pyridine ring gives rise to two broadened singlets in the range 7.37–8.94 ppm. Similar pattern of signals from the amino group was formerly described for 2-amino-6-iodopyridines in [1]. The proton of the furan ring in the ^{1}H NMR spectra of the aryl and the *tert*-butyl derivatives appears as a singlet in the region 5.49–6.96 ppm, and in the spectra of compounds **IVa, IVb** it is observed as a quartet and a triplet respectively. The protons of the methylene unit in compound **IVb** are diastereotopic and appear as two multiplets.

In this process the formation of two position isomers is possible, **IV** and **A,** that differ by the reciprocal location of the amino group and the iodine atom with respect to the rest part of the molecule. In keeping with TLC and ^{1}H NMR spectra only one of the possible isomers forms in the reaction, and its structure was derived from the analysis of the ^{13}C NMR spectrum of compound **IVd**. Informative carbon signals are those of the pyridine ring in the positions *3* and *5*. According to the calculations

* For Communication III, see [1].



R = CH_3 (**a**), C_2H_5 (**b**), *t*-C_4H_9 (**c**), C_6H_5 (**d**), 3-ClC_6H_4 (**e**), 4-ClC_6H_4 (**f**), 2,4-$Cl_2C_6H_3$ (**g**).

performed using the data on the effect of the functional groups on the displacement of the chemical shifts in the ^{13}C NMR spectra of the pyridine ring [12], the signals of atoms C^{3a} and C^{7} of compound **IVd** differ insignificantly (107.4 and 107.8 ppm respectively). Analogous calculations for the alternative structure **A** give values 124.9 (C^{3a}) and 90.3 ppm (C^{7}). In the ^{13}C NMR spectrum of furopyridine **IVd** signals 102.59 and 99.4 ppm correspond to atoms C^{3a} and C^{7} in agreement with the structure **IVd**.

The most probable sequence of transformations consists in the primary formation of a dihydrofuran intermediate. In this stage also the reduction takes place. This is confirmed by the possibility to isolate dihydrofurans **III** as the main reaction product if the reaction mixture is not subjected to boiling. Thus obtained dihydrofurans **III** react at boiling with HI converting into furo[3,4-*c*]pyridines **IV**. In dihydrofurane **III** two types of cyano groups are present: cyano groups of the dicyanomethylene fragment and of enaminonitrile fragment. The regioselectivity of reactions between α,ω-dinitriles and hydrogen halides was investigated in [13–18]. It was suggested that the halogen added to the cyano group bound to an sp^2-hybridized carbon atom. In [13] the regioselectivity was regarded as related to the basicity of the cyano groups, but it was also shown in [13] that the reaction depended on many factors, among them also on the halogen nature, and no such studies concerned HI. Only several publications concern the results of HI reaction with α,ω-dinitriles [15–18], also with unsymmetrical ones [17, 18]. We believe that the direction of the reaction depends not only on the basicity, but also on the electrophilic properties of the cyano group. In the dicyanomethylene fragment it is higher for on the one hand it is less affected by the deactivating influence of the amino group, and on the other hand two adjacent cyano groups mutually increase the reactivity of each other. Therefore the addition of HI occurs regioselectively to the cyano groups of the dicyanomethylene fragment. It is followed by the heterocyclization and isomerization involving the formation of the aromatic system of the pyridine ring, and the amino group at the furan ring is converted into imino group. The latter easily hydrolyses under the reaction conditions.

EXPERIMENTAL

The reaction progress was monitored and the purity of compounds synthesized was checked by TLC on Silufol UV-254 plates (development under UV irradiation in iodine vapor, and at the thermal decomposition). IR spectra were recorded from thin films or mulls in mineral oil

on an IR Fourier spectrophotometer FSM-1202. ^{1}H and ^{13}C NMR spectra were registered on a spectrometer Bruker DRX-500 at operating frequencies 500.13 and 125.76 MHz respectively, solvent DMSO-d_6, internal reference TMS. Mass spectra were obtained on an instrument Simadzu GCMS-QP2010S DI (electron impact, 70 eV).

4-Amino-6-iodo-1-methyl-3-oxo-1,3-dihydrofuro[3,4-*c*]pyridine-7-carbonitrile (IVa). With 15 ml of concn. HI was thoroughly triturated 1.03 g (5 mmol) of propenide **Ia**, then the reaction mixture was heated at 100°C for 1–3 min, the mixture was cooled and diluted with 10 ml of cold water. The separated oily substance was isolated by decanting and triturated at heating with 10 ml of ethanol. The dispersion obtained was filtered, the precipitate was washed with ethanol till the removal of iodine, then it was recrystallized from glacial actic acid (25 ml). Yield 1.23 g (78%), mp 244–246°C. IR spectrum, ν, cm^{-1}: 3342, 3261 (NH_2), 2223 (CN), 1748 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.57 д (3H, CH_3, ^3J 6.8 Hz), 5.74 к (1H, CH, ^3J 6.8 Hz), 7.55 s (1H, NH_2), 8.79 s (1H, NH_2). Mass spectrum, *m/z* (I_{rel}, %): 316 (9) $[M]^+$, 315 (89) $[M]^+$, 188 (57) $[M - I]^+$, 127 (76) $[I]^+$, 117 (58), 90 (100). Found, %: C 34.72; H 1.95; N 13.79. $C_9H_6IN_3O_2$. Calculated, %: C 34.31; H 1.92; N 13.34. *M* 314.95.

Compounds **IVb–IVg** were obtained similarly.

4-Amino-1-ethyl-6-iodo-3-oxo-1,3-dihydrofuro[3,4-*c*]pyridine-7-carbonitrile (IVb). Yield 67%, mp 238–240°C. IR spectrum, ν, cm^{-1}: 3326, 3204 (NH_2), 2225 (C≡N), 1750 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.88 t (3H, CH_3, ^3J 7.3 Hz), 1.76–1.86 m (1H, CH_2), 2.21–2.22 m (1H, CH_2), 5.69 d.d (1H, CH, ^3J 7.3, 3.4 Hz), 7.56 c (1H, NH_2), 8.79 c (1H, NH_2). Mass spectrum, *m/z* (I_{rel}, %): 330 (9) $[M + 1]^+$, 329 (94) $[M]^+$, 301 (6) $[M - 28]^+$, 300 (99) $[M - 29]^+$, 127 (95) $[I]^+$, 116 (47), 117 (44), 90 (85), 55 (100). Found, %: C 36.61; H 2.53; N 12.81. $C_{10}H_8IN_3O_2$. Calculated, %: C 36.50; H 2.45; N 12.77. *M* 328.97.

4-Amino-1-(*tert*-butyl)-6-iodo-3-oxo-1,3-dihydrofuro[3,4-*c*]pyridine-7-carbonitrile (IVc). Yield 73%, mp 236–238°C (decomp.). IR spectrum, ν, cm^{-1}: 3251 (NH_2), 2223 (C≡N), 1752 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.98 s [9H, $C(CH_3)_3$], 5.49 s (1H, CH), 7.57 s (1H, NH_2), 8.80 s (1H, NH_2). Mass spectrum, *m/z* (I_{rel}, %): 357 (3) $[M]^+$, 301 (21), 173 (5), 116 (8), 117 (7), 90 (11), 57 (100). Found, %: C 40.73; H 3.41; N 11.83. $C_{12}H_{12}IN_3O_2$. Calculated, %: C 40.36; H 3.39; N 11.77. *M* 357.00.

4-Amino-6-iodo-3-oxo-1-phenyl-1,3-dihydrofuro[3,4-*c*]pyridine-7-carbonitrile (IVd). Yield 84%, mp 267–269°C (decomp.). IR spectrum, ν, cm^{-1}: 3343, 3222 (NH_2), 2224 (C≡N), 1755 (C=O). ^{1}H NMR spectrum, δ, ppm: 6.71 s (1H, CH), 7.35–7.37 m ($2H_{arom}$), 7.42–7.46 m ($3H_{arom}$), 7.66 s (1H, NH_2), 8.88 s (1H, NH_2). ^{13}C NMR spectrum, δ, ppm: 80.87 (C^1), 99.40 (C^7), 102.59 (C^{3a}), 116.42 (CN), 128.35 (*o*-Ph), 128.85 (*m*-Ph), 129.89 (*p*-Ph), 130.62 (C^6), 133.01 (Ph), 155.88 (C^{7a}), 163.79 (C^4), 167.99 (C^3). Mass spectrum, *m/z* (I_{rel}, %): 278 (2) $[M + 1]^+$, 277 (10) $[M]^+$, 250 (4), 127 (48), 116 (27), 105 (40), 90 (12). Found, %: C 44.81; H 2.28; N 11.24. $C_{14}H_8IN_3O_2$. Calculated, %: C 44.59; H 2.14; N 11.14. *M* 376.97.

4-Amino-1-(3-chlorophenyl)-6-iodo-3-oxo-1,3-dihydrofuro[3,4-*c*]pyridine-7-carbonitrile (IVe). Yield (71%), mp 244–246°C (decomp.). IR spectrum, ν, cm^{-1}: 3371, 3211 (NH_2), 2221 (C≡N), 1753 (C=O). ^{1}H NMR spectrum, δ, ppm: 6.73 s (1H, CH), 7.37 д ($1H_{arom}$, ^3J 7.7 Hz), 7.47 t (1H, C_6H_4, ^3J 7.7 Hz), 7.53–7.55 m ($1H_{arom}$), 7.67 s (1H, NH_2), 8.90 (1H, NH_2). Mass spectrum, *m/z* (I_{rel}, %): 413 (2) 411 (6) $[M]^+$, 213 (15), 178 (23), 177 (20), 151 (28), 139 (48), 127 (59), 116 (22), 113 (35), 111 (71), 90 (36), 75 (100). Found, %: C 40.48; H 1.69; N 10.17. $C_{14}H_7ClIN_3O_2$. Calculated, %: C 40.85; H 1.71; N 10.21. *M* 410.93.

4-Amino-1-(4-chlorophenyl)-6-iodo-3-oxo-1,3-dihydrofuro[3,4-*c*]pyridine-7-carbonitrile (IVf). Yield (68%), mp 220–224°C (decomp.). IR spectrum, ν, cm^{-1}: 3369, 3231 (NH_2), 2221 (C≡N), 1754 (C=O). ^{1}H NMR spectrum, δ, ppm: 6.74 s (1H, CH), 7.44 m (*AA'BB'*, $2H_{arom}$, ^3J 8.4 Hz), 7.51 m (*AA'BB'*, $2H_{arom}$, ^3J 8.4 Hz), 7.68 s (1H, NH_2), 8.89 (1H, NH_2). Mass spectrum, *m/z* (I_{rel}, %): 413 (3) 411 (8) $[M]^+$, 151 (19), 139 (36), 127 (63), 116 (12), 113 (25), 111 (63), 90 (21). Found, %: C 40.78; H 1.73; N 10.24. $C_{14}H_7ClIN_3O_2$. Calculated, %: C 40.85; H 1.71; N 10.21. *M* 410.93.

4-Amino-1-(2,4-dichlorophenyl)-6-iodo-3-oxo-1,3-dihydrofuro[3,4-*c*]pyridine-7-carbonitrile (IVg). Yield (58%), mp 290–292°C (decomp.). IR spectrum, ν, cm^{-1}: 3372, 3211 (NH_2), 2222 (C≡N), 1751 (C=O). ^{1}H NMR spectrum, δ, ppm: 6.96 s (1H, CH), 7.43 br.s (1H, NH_2), 7.50–7.51 m ($1H_{arom}$), 7.74 s ($1H_{arom}$), 7.81 s (1H, $1H_{arom}$), 8.94 (1H, NH_2). Mass spectrum, *m/z* (I_{rel}, %): 449 (1), 448 (1), 447 (10) 446 (2), 445 (15) $[M]^+$, 177 (17), 176 (23), 175 (33), 173 (53), 148 (23), 147 (45), 146 (13), 145 (58), 127 (100), 117 (51), 116 (73), 90 (19). Found, %: C 37.75; H 1.41; N 9.29. $C_{14}H_6Cl_2IN_3O_2$. Calculated, %: C 37.70; H 1.36; N 9.42. *M* 444.89.

REFERENCES

1. Karpov, S.V., Kayukov, Ya.S., Bardasov, I.N., Kayukova, O.V., Lipin, K.V., and Nasakin, O.E*., Zh. Org. Khim.,* 2011, vol. 47, p. 1467.
2. Karpov, S.V., Kayukov, Ya.S., Bardasov, I.N., Kayukova, O.V., Ershov, O.V., and Nasakin, O.E*., Zh. Org. Khim.,* 2011, vol. 47, p. 412.
3. Karpov, S.V., Kayukov, Ya.S., Bardasov, I.N., Ershov, O.V., Nasakin, O.E., and Kayukova, O.V*., Zh. Org. Khim.,* 2011, vol. 47, p. 1144.
4. Kayukov, Ya.S., Bardasov, I.N., Kayukova, O.V., Ershov, O.V., Nasakin, O.E, Eremkin, A.V., and Tafeenko, V.A*., Zh. Org. Khim.,* 2011, vol. 47, p. 717.
5. Bardasov, I.N., Kayukova, O.V., Kayukov, Ya.S., Ershov, O.V., and Nasakin, O.E*., Zh. Org. Khim.,* 2009, vol. 45, p. 1340.
6. Cornett, G.V., Page, J., Jones, W.A., and Page, K., WO, Patent 2008/85872, A1, 2008; *Chem*. *Abstr*., 2008, vol. 149, 143965.
7. Kalinowski, L., Dobrucki, I.T., and Malinski, T., *J. Cardiovascular Pharmy*. , 2001, vol. 37, p. 713.
8. Takahashi, H., Haga, Y., Shibata, T., Nonoshita, K., Sakamoto, T., Moriya, M., Ohe, T., Chiba, M., Mitobe, Y., Kitazawa, H., Iwaasa, H., Ishihara, A., Ishii, Y., Kanatani, A., and Fukami, T., *Bioorg. Med. Chem. Lett.* , 2009, vol. 19, p. 5436,
9. Abe, H., Arai, Y., Aoyagi, S., and Kibayashi, C., *Tetrahedron Lett*., 2003, vol. 44, p. 2971.
10. Haga, Y., Sakamoto, T., Shibata, T., Nonoshita, K., Ishikawa, M., Suga, T., Takahashi, H., Takahashi, T., Takahashi, H., Ando, M., Murai, T., Gomori, A., Oda, Z., Kitazawa, H., Mitobe, Y., Kanesaka, M., Ohe, T., Iwaasa, H., Ishii, Y., Ishihara, A., Kanatani, A., and Fukami, T. *Bioorg. Med. Chem*., 2009, vol. 17, p. 6971.
11. Jitsuoka, M., Tsukahara, D., and Sato, N., WO, Patent 2007055418 A1, 2007; *Chem*. *Abstr*., 2007, vol. 146, 52177.
12. Pretsch, E., Buhlmann, P., and Affolter, C., *Structure Determination of Organic Compounds*, Springer-Verlag, 2000.
13. Teixido, J., Borrell, J.I., Serra, B., Matallana, J.L., Colominas, C., Carrion F., Pascual R., Falco J.L., and Batllori, X., *Heterocycles,* 1999, vol. 50, p. 739.
14. Wan Y., Niu W., Behof W.J., Wang Y., Boyle P., and Gorman C.B., *Tetrahedron,* 2009, vol. 65, p. 4293.
15. Atkinson J.D. and Johnson M.C., *J. Chem. Soc. C.* 1968, p. 1252.
16. Johnson F., Panella J.P., Carlson A.A., and Hunneman D.H., *J. Org. Chem*. 1962, vol. 27, p. 2473.
17. Neumeyer J.L. and Weinhardt K.K. *J. Med. Chem.* 1970, vol. 13, p. 613.
18. Johnson F. and Nasutavicus W.A. *J. Org. Chem*. 1962, vol. 27, p. 3953.