DOI 10.1007/s10593-020-02752-y

Chemistry of Heterocyclic Compounds **2020**, *56*(7), 930–935

Iodine acetate as a mild selective agent for the Wagner–Meerwein rearrangement in 3a,6-epoxyisoindoles

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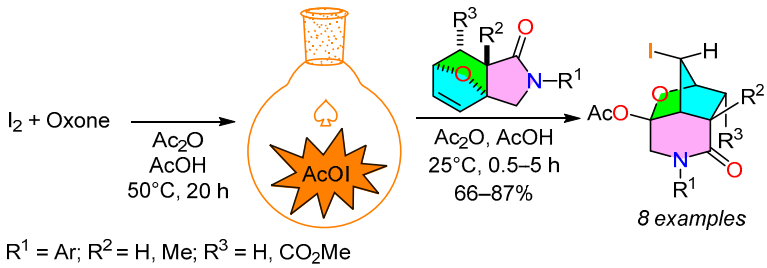
Translated from Khimiya Geterotsiklicheskikh Soedinenii, 2020, *56*(7), 930–935

Submitted April 9, 2020
Accepted May 4, 2020



The iodine-initiated cationic skeletal Wagner–Meerwein rearrangement in tetrahydro-3a,6-epoxyisoindol-1-ones has been studied. It was shown that by the action of iodine acetate in acetic anhydride the reaction proceeds regio- and stereoselectively with the formation of 5-iodo-4,6-epoxycyclopenta[*c*]pyridin-4-yl acetates. The proposed reagent provides better yields of rearrangement products than those described in the literature.

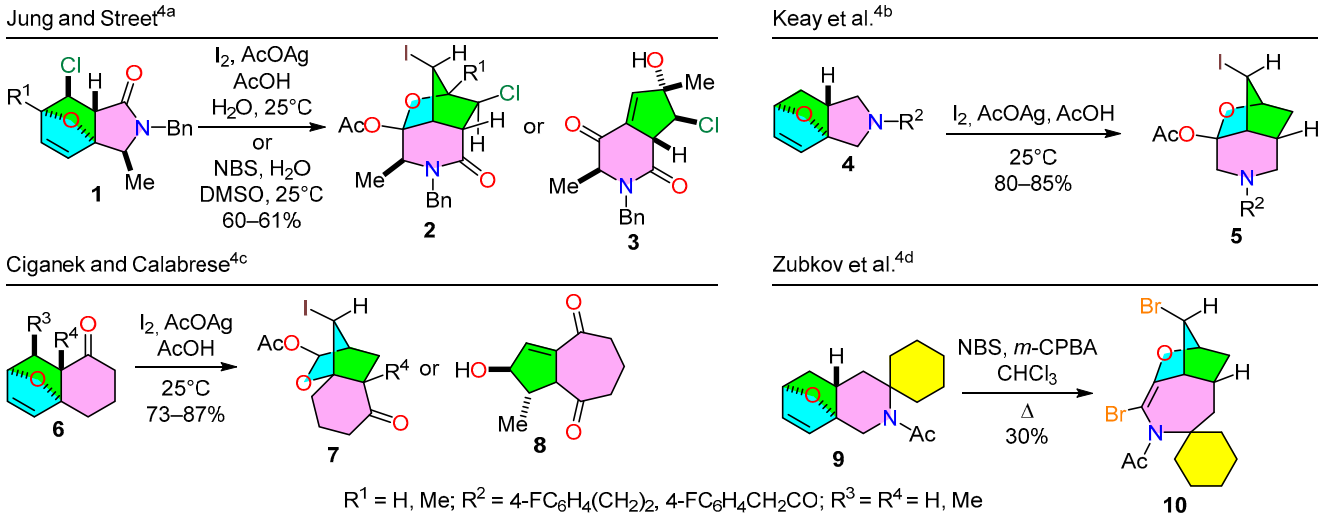
Keywords: cyclopenta[*c*]pyridines, iodine acetate, isoindoles, IMDAF reaction, intramolecular Diels–Alder reaction, Wagner–Meerwein rearrangement.

The Wagner–Meerwein rearrangement was discovered by Wagner in his study of the dehydration of bicyclic terpenes[1a] and was studied in detail in the 1920s by Meerwein,[1b] who proposed the cationic mechanism of this reaction generally accepted today.[1c] A distinctive feature of the process is the [1,2]-sigmatropic shift of a hydrogen atom, an alkyl or aryl substituent; since the bond migrates to an electron-deficient center, the rearrangement is often called anionotropic (sextet or nucleophilic).[2] This type of rearrangement plays an important role in the chemical transformations of nitrogen- and oxygen-containing bridged heterocycles due to the ability to carry out complex transformation of the carbon skeleton in one step, which makes it possible to obtain from relatively simple starting compounds products that are practically inaccessible in other ways.[3]

The halogen-initiated Wagner–Meerwein cationic rearrangement in oxabicycloheptenes[4] coupled with carbon- or nitrogen-containing rings was first demonstrated in 1985, when Young and Street succeeded in transforming tetrahydro-3a,6-epoxyisoindol-1-ones **1** under the conditions of the Prévost–Woodward reaction (I_2/AcOAg/AcOH) or by the action of *N*-bromosuccinimide[4a] (Scheme 1). It was shown that, depending on the electrophilic agent used, rearrangement can lead to both tricyclic compounds **2** and cyclopentapyridine **3**. Subsequently, the conditions found were used to convert 3a,6-epoxyisoindoles **4** into sigma receptor antagonists (structures **5**).[4b] In 1989, Keay et al. studied the iodine-initiated rearrangement of 4a,7-epoxyoctahydronaphthalen-1-ones (**6**). Later, it was shown that, depending on the substituents R^3 and R^4, either tricyclic product **7** or hydrogenated azulene **8**[4c] is formed (Scheme 1). When replacing a carbon atom with a nitrogen atom in carbocycle of 4a,7-epoxyoctahydronaphthalene **9**, the main reaction product turned out to be heterocycle **10**.[4d] Using Br_2 in an alkaline medium, Woodward and Baer carried out a rearrangement using the example of tetrahydro-4,7-epoxybenzofuran-1,3-dione and refuted erroneous statement by Diels and Alder about the formation of an *endo* adduct of furan with maleic anhydride.[5]

Analysis of the presented data does not allow one to reliably predict the direction of the rearrangement. All described examples have been studied on a limited number of substrates, and the use of molecular halogens and

Scheme 1



expensive transition metal salts significantly limits the scope of this method. In this work, we proposed and tested cheap and readily available AcOI as a rearrangement initiator and a source of a positively charged halogen ion. The choice of AcOI,[6] obtained by one-pot synthesis from Oxone and iodine,[6a] is due to its cheapness, simplicity of synthesis and isolation, and the unambiguous direction of rearrangement. In addition, AcOI is an excellent reagent for the functionalization of unsaturated hydrocarbons[6a,c–e] and is also used for other molecular rearrangements[6d,e] in the synthesis of heterocyclic compounds of the pyrrole series[6f] and for modifications of organoelement compounds.[6g]

The present work is aimed at further accumulating experimental data and establishing the rules of the iodine-initiated Wagner–Meerwein rearrangement in bicyclic aza-heterocycles.[7]

The starting compounds were 3a,6-epoxyisoindolones **12a**–**h**, synthesized in two steps according to known methods[3h,8] from furfurylamines **11a**–**f** and maleic anhydride or acryloyl(methacryloyl) chloride (IMDAF reaction, from the IntraMolecular Diels–Alder Reaction of Furan). To improve the solubility in Ac_2O, the carboxylic acid synthesized from furfurylamine **11h** was converted into methyl ester **12h**. Isoindolones **12a**–**h** obtained in this way were isolated as individual diastereomers with the relative configuration of the substituents shown in Scheme 2 (Table 1).

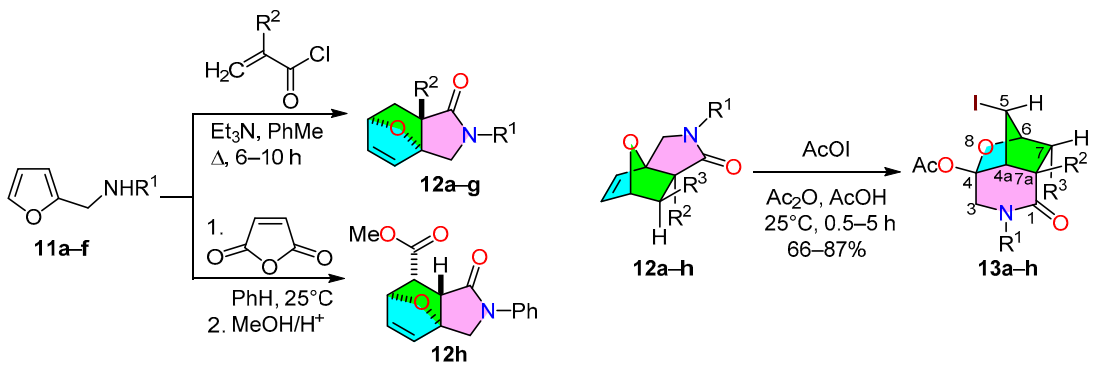
We used AcOI obtained by one-pot synthesis from Oxone and iodine[6a] as an initiator of the Wagner–Meerwein rearrangement of isoindolones **12a**–**h**, which favorably distinguishes the proposed method from the conditions described earlier[4a] (I_2/AcOAg). The reaction of AcOI with 7-oxabicycloheptenes **12a**–**h** (Scheme 2) proceeds quickly and under mild conditions (from 0.5 to 5 h at room temperature). In this case, the products of the skeletal rearrangement, 4,6-epoxycyclopenta[*c*]pyridines **13a**–**h**, are formed, as a rule, in higher yields (Table 1) as compared with the reactions carried out under the conditions of the Prévost–Woodward reaction.[4]

The halogen-initiated transformations of isoindolones **12a**–**h** can proceed in two ways (Scheme 3). Theoretically,

Table 1. Yields of starting epoxyisoindolones **12a**–**h** and products of their rearrangement **13a**–**h**

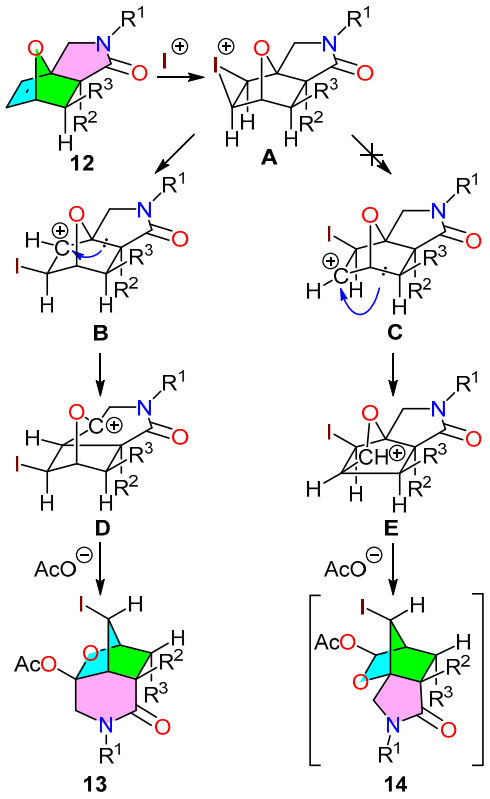
Epoxy-isoindolone	R^1	R^2	R^3	Yield, %	Rearrange-ment product	Yield, %
12a	Ph	H	H	48[3h]	**13a**	87
12b	4-MeC_6H_4	H	H	42	**13b**	77
12c	4-ClC_6H_4	H	H	66	**13c**	75
12d	4-FC_6H_4	H	H	60	**13d**	77
12e	4-$F_3CC_6H_4$	H	H	49	**13e**	71
12f	4-$MeOC_6H_4$	H	H	45	**13f**	71
12g	Ph	Me	H	25[8]	**13g**	67
12h	Ph	H	CO_2Me	83[3h]	**13h**	66

Scheme 2



iodonium ion **A** can transform into two alternative carbocations **B** and **C**, the subsequent migration of neighboring σ-bonds in which leads to the mesomerically stabilized **D** (tertiary) and **E** (secondary) cations. The rearrangement is completed by the addition of acetate anion from the reaction medium to the carbocation sites. Thus, as a result of skeletal rearrangement, the formation of two tricyclic products **13** and **14** is possible.

Scheme 3



It was experimentally established that the sigmatropic rearrangement of isoindolones **12a**–**h**, regardless of substituents R, proceeds chemoselectively *via* intermediate cations **B** and **D**, leading exclusively to epoxycyclopenta[*c*]-pyridines **13a**–**h**. The absence of alternative products **14** can be explained, first, by a more significant decrease in the Baeyer and Pitzer strain of the system during the formation of products **13** (the coupling of two five-membered and six-membered rings in cyclopentapyridines **13** is preferable to a set of three five-membered rings in tricyclic compounds **14**). Second, in cation **C**, the migration of the neighboring σ-bond should be more difficult than in cation **B**, since in cation **B** the migrating bond is additionally included in the pyrrolidone ring, and, therefore, is more strained (less strong) compared to the alternative bond in cation **C**. Third, the direction of migration of the σ-bond is associated with the formation of tertiary carbocation **D** in the second step, which is more stable than secondary cation **E**.

The structure of the rearrangement products epoxycyclopenta[*c*]pyridines **13a**–**h** was established by analogy with previously published studies[3h,3i,7] and additionally confirmed by X-ray structural analysis using one example (Fig. 1). In the ^{1}H NMR spectra, the most characteristic signals of cyclopentapyridines **13a**–**h** include singlet signals of 5-CH protons of the bridge and 6-CH protons in the bridgehead at 3.90–4.26 and 4.66–4.86 ppm, respectively, and also doublets of 4a-CH protons with a coupling constant $J_{4a,7a}$ = 4.0–4.3 Hz in the 3.38–3.72 ppm range. In the carbon spectra, the signals of quaternary carbon atoms C-4 at 103.7–104.7 ppm as well as carbon atoms C-5 at 83.9–86.5 ppm, located in the vicinity of the iodine atom, are most clearly identified.

X-ray structural analysis of a single crystal of compound **13d** confirmed the structure of the product of the sigmatropic rearrangement and the formation of the 4,6-epoxycyclopenta[*c*]pyridine framework (Fig. 1). The molecule contains a flattened piperidone ring in the chair conformation and two five-membered rings, tetrahydrofuran and cyclopentane, joined with it in the envelope conformation. Compound **13d** crystallizes in the triclinic system, *P*1 space group (unit cell parameters are listed in Table 2 in the Supplementary information file). The molecule occupies a common position, the number of formula units per cell is equal to 2. The main bond lengths, bond and torsion angles are given in Tables 3–5 in the Supplementary information file. In the crystal packing, the oxygen atom of the carbonyl group acts as an acceptor of the hydrogen bond with the CH group of the aromatic ring of the neighboring molecule, which was previously observed for molecules with similar structures.[7]

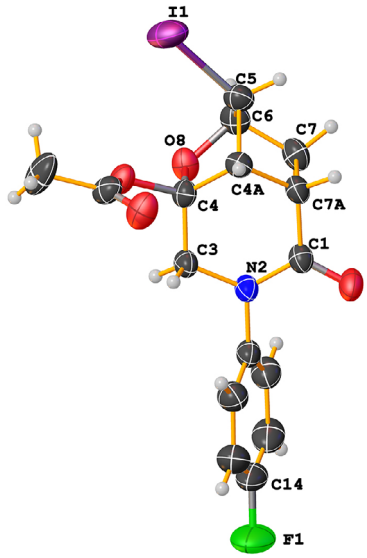


Figure 1. Molecular structure of tricyclic compound **13d**, thermal ellipsoids are at the 50% probability level.

To conclude, in this work it was shown for the first time that iodine acetate generated *in situ* from iodine and Oxone in acetic anhydride medium is a convenient reagent for initiating the Wagner–Meerwein sigmatropic rearrangement in tetrahydro-3a,6-epoxyisoindol-1-ones. It has been found that the reaction proceeds stereo- and chemospecifically, leading to the formation of 5-iodo-4,6-epoxycyclopenta[*c*]pyridin-4-yl acetates in good yields.

Experimental

IR spectra were registered on an Infralum FT-801 Fourier spectrometer in KBr pellets. ^{1}H, ^{13}C, and ^{19}F NMR spectra were acquired on a JEOL JNM-ECA 600 spectrometer (600, 151, and 565 MHz, respectively), Residual signals of deuterated solvents were used as internal standards ($CDCl_3$: 7.26 ppm for ^{1}H nuclei, 77.2 ppm for ^{13}C nuclei; DMSO-d_6: 2.50 ppm for ^{1}H nuclei, 39.5 ppm for ^{13}C nuclei). Mass spectra of compounds **12b–d**,**f** were recorded on a Thermo DSQ II – Focus GC mass spectrometer (EI ionization, 70 eV, 200°C source temperature, helium carrier gas, RTX-5MS column). ESI mass spectra of compounds **12e**, **13a–h** were recorded on an Agilent 6470 mass spectrometer, AJS ESI ionization source (ZORBAX RRHD Eclipse Plus C18 reversed-phase chromatographic column, 3×50 mm, 1.8 μ m, mobile phase – MeCN (70%), H_2O (30%), and HCO_2H (0.2%), 0.4 ml/min flow, 40°C temperature). Elemental analysis was performed on a Euro Vector EA-3000 CHNS-analyzer. Melting points were determined in open capillaries on SMP 10 or SMP 30 apparatuses and are uncorrected. Sorbfil PTSKh-AF-A-UF-254 plates were used for TLC, visualization in iodine vapor or with $KMnO_4$ reagent.

Reagents were supplied by Acros Organics or Alfa Aesar and were used without additional purification. Yields, elemental analysis data, and physicochemical characteristics of compounds **12a**,**g** have been published previously.[3h,8] The synthesis and physicochemical characteristics of ester **12h** have been described earlier.[3h]

Synthesis of 3a,6-epoxy-2,3,7,7a-tetrahydroisoindol-1-ones 12b–f (General method). A solution of the corresponding amine **11a–f** (0.06 mol), acryloyl chloride (7.3 ml, 0.09 mol), and Et_3N (16.7 ml, 0.12 mol) in PhMe (100 ml) was heated under reflux for 6–10 h (TLC control, for compounds **12b**,**c**,**e**,**f**, eluent EtOAc–hexane, 1:1; for compound **12d**, eluent EtOAc–hexane, 2:3). The mixture was cooled and poured into H_2O (100 ml). The organic layer was separated, the aqueous layer was extracted with AcOEt (3×50 ml). The organic fractions were combined and dried over anhydrous $MgSO_4$. The extract was evaporated under reduced pressure, and the residue was recrystallized from a hexane–AcOEt mixture.

(3a*RS*,6*RS*,7a*SR*)-2-(4-Methylphenyl)-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-1(6*H*)-one (12b). Yield 6.07 g (42%), light-yellow powder, mp 152–154°C. IR spectrum, ν, cm^{-1}: 1682 (NCO). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.66 (1H, dd, *J* = 11.9, *J* = 8.8, 7-CH_2); 2.30 (1H, ddd, *J* = 11.9, *J* = 4.7, *J* = 3.5, 7-CH_2); 2.32 (3H, s, CH_3); 2.62 (1H, dd, *J* = 8.8, *J* = 3.5, 7a-CH); 4.10 (1H, d, *J* = 11.4, 3-CH_2); 4.43 (1H, d, *J* = 11.4, 3-CH_2); 5.10 (1H, dd, *J* = 4.7, *J* = 1.5, 6-CH); 6.43 (1H, dd, *J* = 5.9, *J* = 1.5, 5-CH); 6.46 (1H, d, *J* = 5.9, 4-CH); 7.16 (2H, d, *J* = 8.6, H Ar); 7.48 (2H, d, *J* = 8.6, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.0; 28.9; 48.8; 51.1; 79.3; 88.3; 120.5; 129.5; 133.2; 134.5; 137.0; 137.5; 173.4. Mass spectrum, *m*/*z* (I_{rel}, %): 241 $[M]^+$ (100), 212 (11), 186 (10), 107 (8), 91 (9), 81 (99), 55 (42), 53 (16). Found, %: C 74.60; H 6.18; N 5.92. $C_{15}H_{15}NO_2$. Calculated, %: C 74.67; H 6.27; N 5.81.

(3a*RS*,6*RS*,7a*SR*)-2-(4-Chlorophenyl)-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-1(6*H*)-one (12c). Yield 10.36 g (66%), golden plates, mp 163–164°C. IR spectrum, ν, cm^{-1}: 1694 (NCO). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.68 (1H, dd, *J* = 12.1, *J* = 8.6, 7-CH_2); 2.30 (1H, ddd, *J* = 12.1, *J* = 4.5, *J* = 3.5, 7-CH_2); 2.62 (1H, dd, *J* = 8.6, *J* = 3.5, 7a-CH); 4.10 (1H, d, *J* = 11.3, 3-CH_2); 4.42 (1H, d, *J* = 11.3, 3-CH_2); 5.10 (1H, dd, *J* = 4.5, *J* = 1.5, 6-CH); 6.45 (1H, dd, *J* = 5.6, *J* = 1.5, 5-CH); 6.46 (1H, d, *J* = 5.6, 4-CH); 7.31 (2H, d, *J* = 8.8, H Ar); 7.58 (2H, d, *J* = 8.8, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 29.0; 48.8; 50.9; 79.4; 88.0; 121.3; 129.0; 129.8; 133.0; 137.6; 138.1; 173.6. Mass spectrum, *m*/*z* (I_{rel}, %): 263 $[M]^+$ (10), 261 $[M]^+$ (33), 111 (9), 81 (100), 55 (36), 53 (19). Found, %: C 64.18; H 4.56; N 5.44. $C_{14}H_{12}ClNO_2$. Calculated, %: C 64.25; H 4.62; N 5.35.

(3a*RS*,6*RS*,7a*SR*)-2-(4-Fluorophenyl)-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-1(6*H*)-one (12d). Yield 8.82 g (60%), light-yellow powder, mp 117–118°C. IR spectrum, ν, cm^{-1}: 1693 (NCO). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.67 (1H, dd, *J* = 11.6, *J* = 8.6, 7-CH_2); 2.30 (1H, ddd, *J* = 11.6, *J* = 4.5, *J* = 3.5, 7-CH_2); 2.62 (1H, dd, *J* = 8.6, *J* = 3.5, 7a-CH); 4.09 (1H, d, *J* = 11.6, 7-CH_2); 4.43 (1H, d, *J* = 11.6, 7-CH_2); 5.10 (1H, dd, *J* = 4.5, *J* = 1.5, 6-CH); 6.44 (1H, dd, *J* = 5.8, *J* = 1.5, 5-CH); 6.47 (1H, d, *J* = 5.8, 4-CH); 7.05 (2H, dd, *J* = 9.1, *J* = 8.6, H Ar); 7.58 (2H, dd, *J* = 9.1, *J* = 4.5, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 29.0; 48.7; 51.3; 79.4; 88.2; 115.7 (d, *J* = 23.1); 122.2 (d, *J* = 7.2); 133.0; 135.6 (d, *J* = 2.9); 137.6; 159.7 (d, *J* = 244.2); 173.5. Mass spectrum, *m*/*z* (I_{rel}, %): 245 $[M]^+$ (2), 122 (6), 109 (10), 95 (15), 81 (100), 55 (38), 53 (30). Found, %: C 68.49; H 4.88; N 5.83. $C_{14}H_{12}FNO_2$. Calculated, %: C 68.56; H 4.93; N 5.71.

(3a*RS*,6*RS*,7a*SR*)-2-[4-(Trifluoromethyl)phenyl]-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-1(6*H*)-one (12e). Yield 8.67 g (49%), light-yellow powder, mp 196–197°C. IR spectrum, ν, cm^{-1}: 1688 (NCO). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.69 (1H, dd, *J* = 11.8, *J* = 8.8, 7-CH_2); 2.31 (1H, ddd, *J* = 11.8, *J* = 4.5, *J* = 3.5, 7-CH_2); 2.65 (1H, dd, *J* = 8.8, *J* = 3.5, 7a-CH); 4.17 (1H, d, *J* = 11.6, 3-CH_2); 4.46 (1H, d, *J* = 11.6, 3-CH_2); 5.10 (1H, dd, *J* = 4.5, *J* = 1.5, 6-CH); 6.45 (1H, dd, *J* = 6.1, *J* = 1.5, 5-CH); 6.47 (1H, d, *J* = 6.1, 4-CH); 7.60 (2H, d, *J* = 8.6, H Ar); 7.79 (2H, d, *J* = 8.6, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 29.2; 49.0; 50.7; 79.4; 87.9; 119.4; 124.2 (q, *J* = 271.7); 126.1 (q, *J* = 33.2); 126.2 (q, *J* = 4.3); 132.9; 137.8; 142.5; 174.0. Mass spectrum, *m*/*z* 296 $[M+H]^+$. Found, %: C 60.96; H 4.02; N 4.82. $C_{15}H_{12}F_3NO_2$. Calculated, %: C 61.02; H 4.10; N 4.74.

(3a*RS*,6*RS*,7a*SR*)-2-(4-Methoxyphenyl)-2,3,7,7a-tetrahydro-3a,6-epoxyisoindol-1(6*H*)-one (12f). Yield 6.94 g (45%), light-yellow powder, mp 123–124°C. IR spectrum, ν, cm^{-1}: 1679 (NCO). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.65 (1H, dd, *J* = 11.9, *J* = 8.8, 7-CH_2); 2.28 (1H, ddd, *J* = 11.9, *J* = 4.5, *J* = 3.5, 7-CH_2); 2.60 (1H, dd, *J* = 8.8, *J* = 3.5, 7a-CH); 3.78 (3H, s, CH_3); 4.06 (1H, d, *J* = 11.6, 3-CH_2); 4.41 (1H, d, *J* = 11.6, 3-CH_2); 5.09 (1H, dd, *J* = 4.5, *J* = 1.5, 6-CH); 6.42 (1H, dd, *J* = 5.8, *J* = 1.5, 5-CH); 6.45 (1H, d, *J* = 5.8, 4-CH); 6.89 (2H, d, *J* = 9.1, H Ar); 7.49 (2H, d, *J* = 9.1, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 28.8; 48.6; 51.5; 55.6; 79.3; 88.3; 114.2; 122.4; 132.6; 133.2; 137.4; 156.9; 173.3. Mass spectrum, *m*/*z*

(I_{rel}, %): 257 $[M]^+$ (15), 176 (6), 123 (7), 95 (11), 81 (77), 55 (100), 53 (32). Found, %: C 69.95; H 5.80; N 5.53. $C_{15}H_{15}NO_3$. Calculated, %: C 70.02; H 5.88; N 5.44.

Synthesis of 5-iodo-4,6-epoxycyclopenta[*c*]pyridin-4-yl acetates 13a–h (General method). A suspension of iodine (0.32 g, 1.25 mmol) and Oxone (1.54 g, 2.5 mmol) in a mixture of Ac_2O (7.55 ml, 80 mmol) and AcOH (7.4 ml, 130 mmol) was stirred at 50°C in a flask shielded from light for 20 h until complete discoloration of the solution. The mixture was then cooled to room temperature, and the corresponding isoindolone **12a**–**h** (2 mmol) was added. The reaction mixture was stirred for 0.5–5 h (TLC control, eluents: for compound **13a**, EtOAc–hexane, 1:2; for compounds **13b**,**c**,**e**,**f**,**h**, EtOAc–hexane, 1:1; for compound **13d**, EtOAc–hexane, 2:3; for compound **13g**, EtOAc–hexane, 1:3), poured into H_2O (50 ml), neutralized with K_2CO_3, extracted with CH_2Cl_2 (3×25 ml). The combined organic fractions were dried over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure, and the residue was recrystallized from a hexane–AcOEt mixture.

(4*SR*,4a*RS*,5*SR*,6*RS*,7a*SR*)-5-Iodo-2-phenyl-1-oxooctahydro-4*H*-4,6-epoxycyclopenta[*c*]pyridin-4-yl acetate (13a). Yield 0.7 g (87%), light-beige powder, mp >157°C. IR spectrum, ν, cm^{-1}: 1737, 1670 (NCO, OCO), 597 (CI). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.84 (1H, dd, *J* = 13.1, *J* = 4.3, 7-CH_2); 2.13 (3H, s, CH_3); 2.41 (1H, dd, *J* = 13.1, *J* = 11.3, 7-CH_2); 3.08 (1H, dt, *J* = 11.3, *J* = 4.3, 7a-CH); 3.38 (1H, d, *J* = 4.3, 4a-CH); 3.91 (1H, br. s, 5-CH); 4.16 (1H, d, *J* = 13.1, 3-CH_2); 4.16 (1H, d, *J* = 13.1, 3-CH_2); 4.71 (1H, br. s, 6-CH); 7.24–7.31 (3H, m, H Ar); 7.41 (2H, t, *J* = 7.6, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 17.9; 22.3; 36.9; 38.1; 46.6; 54.7; 84.3; 104.1; 126.1; 127.5; 129.4; 140.8; 169.1; 169.2. Mass spectrum, *m*/*z*: 414 $[M+H]^+$. Found, %: C 46.45; H 3.83; N 3.47. $C_{16}H_{16}INO_4$. Calculated, %: C 46.51; H 3.90; N 3.39.

(4*SR*,4a*RS*,5*SR*,6*RS*,7a*SR*)-5-Iodo-2-(4-methylphenyl)-1-oxooctahydro-4*H*-4,6-epoxycyclopenta[*c*]pyridin-4-yl acetate (13b). Yield 0.66 g (77%), colorless powder, mp 150–151°C. IR spectrum, ν, cm^{-1}: 1732, 1667 (NCO, OCO), 600 (CI). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.83 (1H, dd, *J* = 12.8, *J* = 4.3, 7-CH_2); 2.13 (3H, s, CH_3); 2.35 (3H, s, CH_3); 2.40 (1H, t, *J* = 12.8, 7-CH_2); 3.07 (1H, dt, *J* = 12.8, *J* = 4.3, 7a-CH); 3.72 (1H, d, *J* = 4.3, 4a-CH); 3.91 (1H, br. s, 5-CH); 4.13 (1H, d, *J* = 13.1, 3-CH_2); 4.17 (1H, d, *J* = 13.1, 3-CH_2); 4.71 (1H, br. s, 6-CH); 7.12 (2H, d, *J* = 8.1, H Ar); 7.21 (2H, d, *J* = 8.1, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 18.0; 21.0; 22.3; 36.9; 38.0; 46.6; 54.8; 84.3; 104.2; 125.9; 130.0; 137.4; 138.2; 169.1; 169.2. Mass spectrum, *m*/*z* 428 $[M+H]^+$. Found, %: C 47.71; H 4.18; N 3.40. $C_{17}H_{18}INO_4$. Calculated, %: C 47.79; H 4.25; N 3.28.

(4*SR*,4a*RS*,5*SR*,6*RS*,7a*SR*)-2-(4-Chlorophenyl)-5-iodo-1-oxooctahydro-4*H*-4,6-epoxycyclopenta[*c*]pyridin-4-yl acetate (13c). Yield 0.67 g (75%), colorless plates, mp 172–173°C (decomp.). IR spectrum, ν, cm^{-1}: 1735, 1661 (NCO, OCO), 599 (CI). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.58 (1H, dd, *J* = 12.6, *J* = 4.3, 7-CH_2); 2.03 (3H, s, CH_3); 2.33 (1H, dd, *J* = 12.6, *J* = 11.6, 7-CH_2); 2.97 (1H, dt, *J* = 11.6, *J* = 4.3, 7a-CH); 3.55 (1H, d, *J* = 4.3, 4a-CH); 4.10 (1H, d, *J* = 12.8, 3-CH_2); 4.15 (1H, d, *J* = 12.8, 3-CH_2); 4.22 (1H, br. s, 5-CH); 4.66 (1H, br. s, 6-CH); 7.33 (2H, d, *J* = 8.8, H Ar); 7.45 (2H, d, *J* = 8.8, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 19.8; 22.1; 36.0; 37.2; 46.8; 53.6; 84.0; 103.7; 127.8; 128.8; 130.9; 140.3; 168.4; 169.1. Mass spectrum, *m*/*z*: 448 $[M+H]^+$, 450 $[M+H]^+$. Found, %: C 42.86; H 3.30; N 3.24. $C_{16}H_{15}ClINO_4$. Calculated, %: C 42.93; H 3.38; N 3.13.

(4*SR*,4a*RS*,5*SR*,6*RS*,7a*SR*)-2-(4-Fluorophenyl)-5-iodo-1-oxooctahydro-4*H*-4,6-epoxycyclopenta[*c*]pyridin-4-yl-acetate (13d). Yield 0.67 g (77%), colorless prisms, mp 168–169°C (decomp.). IR spectrum, ν, cm^{-1}: 1737, 1661 (NCO, OCO), 597 (CI). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.58 (1H, dd, *J* = 11.6, *J* = 4.0, 7-CH_2); 2.33 (1H, t, *J* = 11.6, 7-CH_2); 2.03 (3H, s, CH_3); 2.97 (1H, dt, *J* = 11.6, *J* = 4.0, 7a-CH); 3.55 (1H, d, *J* = 4.0, 4a-CH); 4.12 (2H, br. s, 3-CH_2); 4.22 (1H, br. s, 5-CH); 4.66 (1H, br. s, 6-CH); 7.22 (2H, t, *J* = 8.3, H Ar); 7.32–7.34 (2H, m, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 19.8; 22.1; 35.9; 37.1; 46.8; 54.2; 83.9; 103.7; 115.6 (d, *J* = 23.1); 128.3 (d, *J* = 8.7); 137.7 (d, *J* = 2.9); 161.0 (d, *J* = 242.7); 168.4; 169.1. ^{19}F NMR spectrum (DMSO-d_6), δ, ppm: –115.1. Mass spectrum, *m*/*z*: 432 $[M+H]^+$. Found, %: C 44.51; H 3.44; N 3.34. $C_{16}H_{15}FINO_4$. Calculated, %: C 44.57; H 3.51; N 3.25.

(4*SR*,4a*RS*,5*SR*,6*RS*,7a*SR*)-5-Iodo-2-[4-(trifluoromethyl)-phenyl]-1-oxooctahydro-4*H*-4,6-epoxycyclopenta[*c*]pyridin-4-yl acetate (13e). Yield 0.68 g (71%), colorless rhombuses, mp 155–156°C (decomp.). IR spectrum, ν, cm^{-1}: 1736, 1661 (NCO, OCO), 601 (CI). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.61 (1H, d, *J* = 12.6, 7-CH_2); 2.04 (3H, s, CH_3); 2.35 (1H, t, *J* = 12.6, 7-CH_2); 3.01 (1H, dd, *J* = 12.6, *J* = 4.0, 7a-CH); 3.58 (1H, t, *J* = 4.0, 4a-CH); 4.15 (1H, dd, *J* = 12.9, *J* = 3.5, 3-CH_2); 4.23 (1H, dd, *J* = 12.9, *J* = 3.5, 3-CH_2); 4.23 (1H, br. s, 5-CH); 4.68 (1H, br. s, 6-CH); 7.55 (2H, d, *J* = 8.7, H Ar); 7.76 (2H, d, *J* = 8.7, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 19.7; 22.1; 36.0; 37.4; 46.9; 53.1; 84.0; 103.7; 124.0 (q, *J* = 271.6); 125.8 (q, *J* = 4.3); 126.3; 126.6 (q, *J* = 33.2); 145.0; 168.4; 169.4. ^{19}F NMR spectrum (DMSO-d_6), δ, ppm: –60.7. Mass spectrum, *m*/*z*: 482 $[M+H]^+$. Found, %: C 42.35; H 3.07; N 3.03. $C_{17}H_{15}F_3INO_4$. Calculated, %: C 42.43; H 3.14; N 2.91.

(4*SR*,4a*RS*,5*SR*,6*RS*,7a*SR*)-5-Iodo-2-(4-methoxyphenyl)-1-oxooctahydro-4*H*-4,6-epoxycyclopenta[*c*]pyridin-4-yl acetate (13f). Yield 0.63 g (71%), colorless prisms, mp 168–170°C. IR spectrum, ν, cm^{-1}: 1729, 1654 (NCO, OCO). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.81 (1H, dd, *J* = 13.3, *J* = 4.3, 7-CH_2); 2.12 (3H, s, CH_3); 2.39 (1H, dt, *J* = 13.3, *J* = 11.6, 7-CH_2); 3.07 (1H, dt, *J* = 11.6, *J* = 4.3, 7a-CH); 3.71 (1H, d, *J* = 4.3, 4a-CH); 3.80 (3H, s, OCH_3); 3.90 (1H, br. s, 5-CH); 4.11 (1H, d, *J* = 13.1, 3-CH_2); 4.16 (1H, d, *J* = 13.1, 3-CH_2); 4.70 (1H, br. s, 6-CH); 6.91 (2H, d, *J* = 8.8, H Ar); 7.16 (2H, d, *J* = 8.8, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 18.0; 22.3; 36.9; 37.9; 46.5; 55.1; 55.4; 77.2; 84.3; 104.1; 114.6; 127.3; 133.5; 158.6; 169.2. Mass spectrum, *m*/*z*: 444 $[M+H]^+$. Found, %: C 46.00; H 4.01; N 3.27. $C_{17}H_{18}INO_5$. Calculated, %: C 46.07; H 4.09; N 3.16.

(4*SR*,4a*RS*,5*SR*,6*RS*,7a*SR*)-5-Iodo-7a-methyl-2-phenyl-1-oxooctahydro-4*H*-4,6-epoxycyclopenta[*c*]pyridin-4-yl acetate (13g). Yield 0.57 g (67 %), light-orange powder, mp 151–152°C (decomp.). IR spectrum, ν, cm^{-1}: 1730,

1653 (NCO, OCO), 602 (CI). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.51 (3H, s, CH_3); 1.86 (1H, d, *J* = 13.3, 7-CH_2); 2.05 (1H, d, *J* = 13.3, 7-CH_2); 2.14 (3H, s, CH_3); 3.49 (1H, br. s, 4a-CH); 4.07 (1H, d, *J* = 12.6, 3-CH_2); 4.25 (1H, d, *J* = 12.6, 3-CH_2); 4.26 (1H, br. s, 5-CH); 4.69 (1H, br. s, 6-CH); 7.23 (2H, d, *J* = 8.6, H Ar); 7.28 (1H, t, *J* = 8.6, H Ar); 7.40 (2H, t, *J* = 8.6, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 17.5; 22.4; 23.9; 41.5; 46.0; 52.3; 53.2; 84.5; 104.1; 126.0; 127.3; 129.2; 141.4; 169.4; 171.4. Mass spectrum, *m*/*z*: 428 $[M+H]^+$. Found, %: C 47.73; H 4.20; N 3.37. $C_{17}H_{18}INO_4$. Calculated, %: C 47.79; H 4.25; N 3.28.

Methyl (4*SR*,4a*RS*,5*SR*,6*RS*,7*RS*,7a*SR*)-4-acetoxy-5-iodo-2-phenyl-1-oxooctahydro-1*H*-4,6-epoxycyclopenta[*c*]pyridine-7-carboxylate (13h). Yield 0.62 g (66%), colorless powder, mp 146–147°C. IR spectrum, ν, cm^{-1}: 1745, 1658 (NCO, OCO), 599 (CI). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.13 (3H, s, CH_3); 3.30–3.35 (2H, m, 7a,4a-CH); 3.67 (1H, d, *J* = 3.0, 7-CH); 3.74 (3H, s, OCH_3); 3.97 (1H, d, *J* = 13.6, 3-CH_2); 4.43 (1H, d, *J* = 13.6, 3-CH_2); 4.03 (1H, br. s, 5-CH); 4.86 (1H, br. s, 6-CH); 7.29–7.32 (1H, m, H Ar); 7.40–7.44 (4H, m, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.1; 16.4; 21.0; 21.9; 40.5; 48.3; 52.4; 58.4; 86.5; 104.7; 126.5; 127.5; 129.3; 141.1; 167.7; 168.8. Mass spectrum, *m*/*z*: 472 $[M+H]^+$. Found, %: C 45.82; H 3.78; N 3.06. $C_{18}H_{18}INO_6$. Calculated, %: C 45.88; H 3.85; N 2.97.

X-ray structural analysis of compound 13d was carried out at room temperature on a Bruker Kappa Apex II automatic four-circle diffractometer with a two-dimensional detector. The cell parameters were refined over the whole data set.[9] The experimental reflection intensities were corrected for absorption using the SADABS program.[10] The structures were solved with the direct method according to the SHELXS program[11] and refined against F^2 by the least-squares technique in the full-matrix anisotropic approximation for all non-hydrogen atoms using the SHELXL-2018 program.[12] The positions of H atoms were calculated geometrically with isotropic temperature factors equal to 1.2 (CH or CH_2 groups) or 1.5 (CH_3 group) of the equivalent isotropic factor of the C atom with which the H atoms are bonded. The experimental parameters and the final probability factor values are given in Table 2 (Supplementary information file). Atomic coordinates and temperature parameters of the crystalline structure were deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1994943).

Supplementary information file containing ^{1}H and ^{13}C NMR spectra of compounds **12b**–**f** and **13a**–**h**, as well as crystallographic data of compound **3d** is available at the journal website at http://link.springer.com/journal/10593.

This work was supported by the Russian Science Foundation (grant 18-13-00456).

*X-ray structural analysis of compound **13d** was carried out at the Center for Collective Use of Physical Methods of Investigation, Frumkin Institute of Physical Chemistry and Electrochemistry (CKP FMI IPCE RAS).*

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