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Reaction of Substituted Methyl 2,3,7-Triazabicyclo[3.3.0]oct-3-ene-4-carboxylates and 1,2,7-Triazaspiro[4.4]non-2-ene-3-carboxylates with Iodinating Agents

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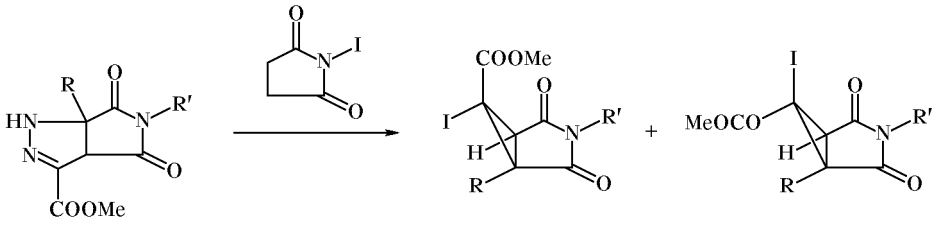
Abstract—Substituted methyl 2,3,7-triazabicyclo[3.3.0]oct-3-ene-4-carboxylates and 1,2,7-triazaspiro[4.4]-non-2-ene-3-carboxylates react with *N*-iodosuccinimide (or the system iodine–silver trifluoroacetate) to give, respectively, methyl 6-iodo-3-azabicyclo[3.1.0]hexane-6-carboxylates or methyl 1-iodo-4,6-dioxo-5-azaspiro-[2.4]heptane-1-carboxylates as mixtures of *exo* and *endo* isomers.

The most widespread methods for the synthesis of 1-iodocyclopropanecarboxylic acid esters are the following: (1) reaction of iodine with 1-lithiated cyclopropanecarboxylates which are prepared by treatment of cyclopropanecarboxylates with *tert*-butyllithium [1] and (2) reaction of olefins with diazoiodoacetates [2]. We previously found that the reaction of substituted 6,8-dioxo-2,3,7-triazabicyclo[3.3.0]oct-3-ene-4-carboxylates and 6,8-dioxo-1,2,7-triazaspiro-[4.4]non-2-ene-3-carboxylates with halogens (chlorine and bromine) yields the corresponding 1-halocyclopropanecarboxylic acid esters [3, 4].

In the present work we studied the reaction of substituted methyl 6,8-dioxo-2,3,7-triazabicyclo-[3.3.0]oct-3-ene-4-carboxylates **Ia**–**Ir** and 6,8-dioxo-1,2,7-triazaspiro[4.4]non-2-ene-3-carboxylates **IIa**–**IIe** with iodinating agents, *N*-iodosuccinimide (NIS) and the system iodine–silver trifluoroacetate. *N*-Iodosuccinimide is known as an effective reagent in electrophilic iodination of unsaturated compounds, in particular of alkenes [5] and alkynes [6]. We have found that the reaction of fused pyrazoles **Ia**–**Ir** with NIS leads to formation of substituted methyl 6-iodo-2,4-dioxo-3-azabicyclo[3.1.0]hexane-6-carboxylates as mixtures of *endo* (**IIIa**–**IIIr**) and *exo* isomers (**IVa**–**IVr**) (Scheme 1). The yields of the products range from 20 to 90%, depending on the substituent at the bridgehead carbon atom. The reactions were carried out in glacial acetic acid at 80°C (compounds **Id**–**Ir**) or 118°C (**Ia**–**Ic**) using 1.5 equiv of NIS. Our attempts to separate *exo* and *endo* isomers **III** and **IV** were unsuccessfull. However, we succeeded in

Scheme 1.



Ia–Ir **IIIa–IIIr** **IVa–IVr**

I, **III**, **IV**, R = H, R′ = Ph (**a**), 3-MeOC$_6$H$_4$ (**b**), 4-ClC$_6$H$_4$ (**c**); R = Me, R′ = Ph (**d**), 4-MeC$_6$H$_4$ (**e**), 4-ClC$_6$H$_4$ (**f**); R = R′ = Ph (**g**); R = Ph, R′ = 4-MeC$_6$H$_4$ (**h**), 4-ClC$_6$H$_4$ (**i**); R = 4-MeC$_6$H$_4$, R′ = Ph (**j**), 4-MeC$_6$H$_4$ (**k**), 4-ClC$_6$H$_4$ (**l**); R = 4-ClC$_6$H$_4$, R′ = Ph (**m**), 4-MeC$_6$H$_4$ (**n**), 4-ClC$_6$H$_4$ (**o**); R = 3-NO$_2$C$_6$H$_4$, R′ = Ph (**p**), 4-MeC$_6$H$_4$ (**q**), 4-ClC$_6$H$_4$ (**r**).

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Table 1. Yields, melting points, and elemental analyses of newly synthesized compounds

Comp. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
IIIa	26	135–136	41.76	2.86	3.49	$C_{13}H_{10}INO_4$	42.07	2.72	3.77
IIIb/IVb	23	–[a]	41.92	3.01	3.49	$C_{14}H_{12}INO_5$	41.92	3.01	3.49
IIIc	31	158–159	38.61	2.42	3.13	$C_{13}H_9ClINO_4$	38.50	2.24	3.45
IVd	31	170–171	43.73	3.33	3.29	$C_{14}H_{12}INO_4$	43.66	3.14	3.64
IVe	19	122–123	45.16	3.68	3.43	$C_{15}H_{14}INO_4$	45.13	3.53	3.51
IVf	20	125–126	40.04	2.80	3.03	$C_{14}H_{11}ClINO_4$	40.07	2.64	3.34
IVg	24	140–141	50.82	3.21	2.96	$C_{19}H_{14}INO_4$	51.03	3.16	3.13
IVh	40	142–143	51.76	3.72	2.96	$C_{20}H_{16}INO_4$	52.08	3.50	3.04
IVi	30	154–155	47.38	2.73	2.78	$C_{19}H_{13}ClINO_4$	47.38	2.72	2.91
IVj	42	127–128	52.04	3.50	2.92	$C_{20}H_{16}INO_4$	52.08	3.50	3.04
IVk	39	153–154	53.29	3.90	2.85	$C_{21}H_{18}INO_4$	53.07	3.82	2.95
IVl	39	129–130	48.62	3.02	2.71	$C_{20}H_{15}ClINO_4$	48.46	3.05	2.83
IVm	50	156–157	47.44	2.94	2.84	$C_{19}H_{13}ClINO_4$	47.38	2.72	2.91
IVn	60	154–156	48.41	3.17	2.34	$C_{20}H_{15}ClINO_4$	48.46	3.05	2.83
IVo	55	135–136	44.50	2.56	2.63	$C_{19}H_{12}Cl_2INO_4$	44.22	2.34	2.71
IIIp/IVp	93	–[b]	46.17	3.07	5.22	$C_{19}H_{13}IN_2O_6$	46.36	2.66	5.69
IIIq/IVq	63	–[b]	47.35	3.21	5.15	$C_{20}H_{15}IN_2O_6$	47.45	2.99	5.53
IIIr/IVr	92	–[b]	43.40	2.71	5.01	$C_{19}H_{12}ClIN_2O_6$	43.33	2.30	5.32
IIIs/IVs	65	–[b]	44.38	2.62	5.20	$C_{20}H_{14}ClIN_2O_6$	44.43	2.61	5.18
VIa	35	175–176	43.51	3.19	3.72	$C_{14}H_{12}INO_4$	43.66	3.14	3.64
Vb/VIb	38	–[a]	44.99	3.58	3.39	$C_{15}H_{14}INO_4$	45.13	3.53	3.51
Vc/VIc	38	–[a]	46.39	4.01	3.28	$C_{16}H_{16}INO_4$	46.51	3.90	3.39
VId	56	165–166	41.47	3.18	2.99	$C_{15}H_{13}ClINO_4$	41.55	3.02	3.23
VIe	42	135–136	36.11	2.44	2.91	$C_{14}H_{11}BrINO_4$	36.24	2.39	3.02
VIf	55	160–161	36.99	2.29	2.93	$C_{14}H_{10}Cl_2INO_4$	37.03	2.22	3.08

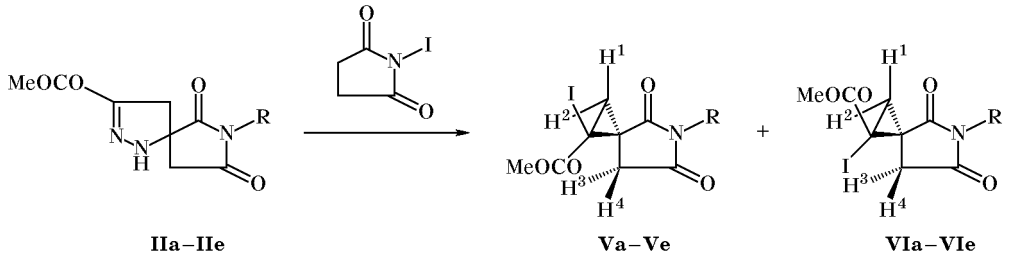
[a] Oily substance.
[b] Amorphous substance.

isolating pure esters **IIIa**, **IIIc**, and **IVd**–**IVo** by recrystallization of the isomer mixture from methanol. The structure of esters **IIIa**–**IIIr** and **IVa**–**IVr** was confirmed by elemental analyses (Table 1) and spectral data (Table 2).

Compounds **Ia**–**Ic** having no substituent in the bridgehead position (R = H) reacted with NIS to give predominantly iodocyclopropanes **IIIa**–**IIIc** with *endo* arrangement of the ester group. By contrast, the corresponding *exo* isomers **IVd**–**IVr** were formed as the major product from esters **Id**–**If** (R = Me) and **Ig**–**Ir** (R = Ar). The **III**-to-**IV** isomer ratios were as follows: 4.9:1 (**a**), 3.2:1 (**b**), 3.9:1 (**c**), 1:6.2 (**d**), 1:5.9 (**e**), 1:7.6 (**f**), 1:6.5 (**g**), 1:7.1 (**h**), 1:6.1 (**i**), 1:7.7 (**j**), 1:6.3 (**k**), 1:5.9 (**l**), 1:6.3 (**m**), 1:6.8 (**n**), 1:5.7 (**o**), 1:5.4 (**p**), 1:5.4 (**q**), and 1:5.6 (**r**). In the ^{1}H NMR spectra of esters **IIIa**–**IIIr** and **IVa**–**IVr** the position of the 5-H signal depends on the R substituent: when R is a hydrogen atom or methyl group, the signal is located at δ 3.14–3.20 ppm (*exo* isomers **IVa**–**IVf**) or 2.77–3.10 ppm (*endo* isomers **IIIa**–**IIIf**); when R is an aryl group, the 5-H signal shifts downfield due to deshielding effect of that group: δ 3.77–3.90 (*exo* isomers **IVg**–**IVr**) and 3.35–3.51 ppm (*endo* isomers **IIIg**–**IIIr**). Signals from the cyclopropane carbon atoms appear in the ^{13}C NMR spectra in the regions of δ_C 45–46 (C^1), 34–36 (C^5), and 15–17 ppm (C^6) for the *exo* isomers and at δ_C 39–41 (C^1), 34–36 (C^5), and 13–15 ppm (C^6) for the *endo* isomers. The structure of compound **IVh** was confirmed by the data of X-ray analysis (see figure). Pyrazole derivatives **I** having an aryl substituent on the bridgehead carbon atom (R = Ar) reacted with NIS at a higher rate and with greater yield than those with R = H or Me.

Spiro esters **IIa**–**IIe** reacted with NIS in glacial acetic acid at 80°C to afford 35–56% of substituted

Scheme 2.

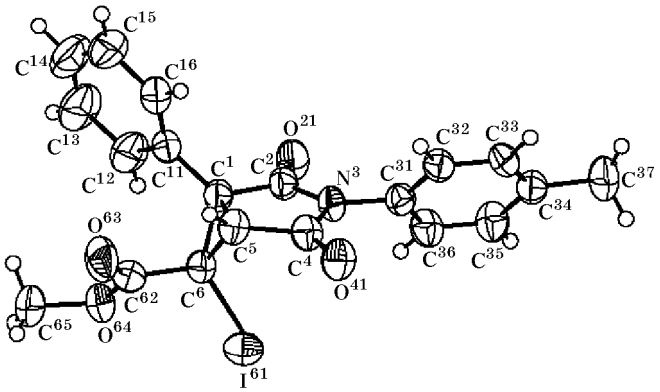


IIa–IIe **Va–Ve** **VIa–VIe**

II, **V**, **VI**, R = Ph (**a**), 4-MeC_6H_4 (**b**), 3,4-$Me_2C_6H_3$ (**c**), 3-Cl-4-MeC_6H_3 (**d**), 4-BrC_6H_4 (**e**).

methyl 1-iodo-4,6-dioxo-5-azaspiro[2.4]heptane-1-carboxylates as mixtures of *syn* (**Va**–**Ve**) and *anti* isomers (**VIa**–**VIe**) (Scheme 2). The isomer ratios **V**:**VI** were 1:2.3 (**a**), 1:2.2 (**b**), 1:2.1 (**c**), 1:3.4 (**d**), and 1:2.1 (**e**). We failed to separate the isomer mixtures by chromatographic methods. Pure esters **VIa**, **VId**, and **VIe** were isolated by recrystallization from methanol. The structure of esters **V** and **VI** was confirmed by elemental analyses (Table 1) and spectral data (Table 2).

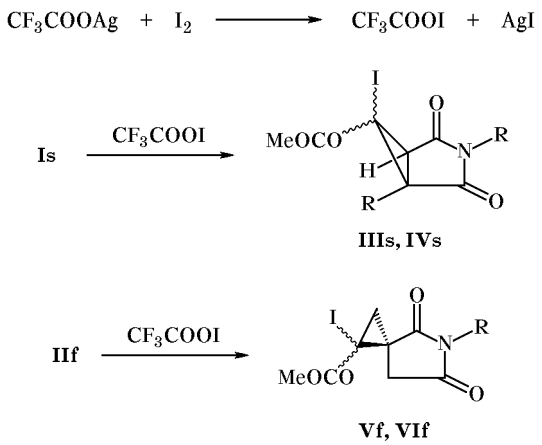
The ^{1}H NMR spectra of compounds **V** and **VI** contain signals from the cyclopropane methylene group, δ, ppm: 2.4 d (H^1, J = 6 Hz, **Va**–**Ve**), 2.8 d (H^1, J = 7 Hz, **VIa**–**VIe**), 2.0 d (H^2, J = 6 Hz, **Va**–**Ve**), ~1.6 d (H^2, J = 7 Hz, **VIa**–**VIe**). Protons of the methylene group in the pyrrolidine ring (H^3 and H^4) appear at δ, ppm: 3.05 d (H^3, J = 19 Hz, **Va**–**Ve**), ~3.3 d (H^3, J = 19 Hz, **VIa**–**VIe**), ~2.8 d (H^4, J = 19 Hz, **Va**–**Ve**), ~3.0 d (H^4, J = 19 Hz, **VIa**–**VIe**). Also, signals from aromatic protons and ester methyl group were present. In the ^{13}C NMR spectra of esters **V** and **VI**, signals from the cyclopropane carbon atoms are located at δ_C, ppm: *syn* isomers **Va**–**Ve**: 3.2 (C^1), 29.6 (C^2), 31.8 (C^3); *anti* isomers **VIa**–**VIe**: 9.6 (C^1), 30.1 (C^2), 31.9 (C^3).



Structure of molecule **IVh** according to the X-ray diffraction data.

We also examined the reaction of bicyclic and spirocyclic dihydropyrazole derivatives, namely esters **Is** and **IIf** with the iodinating system iodine–silver trifluoroacetate. According to published data, silver trifluoroacetate reacts with iodine in nitrobenzene or chlorinated hydrocarbons to give unstable and reactive trifluoroacetyl hypoiodite CF_3COOI (Scheme 3). This compound is capable of iodinating benzene and its derivatives [7], veratrol [8], benzoic acid, and other aromatic compounds [9]. The reaction of methyl 7-(3-chloro-4-methylphenyl)-1-(3-nitrophenyl)-6,8-dioxo-2,3,7-triazabicyclo[3.3.0]oct-3-ene-4-carboxylate (**Is**) with I_2–CF_3COOAg in dichloroethane at 80°C gave 64% of methyl 6-iodo-3-(3-chloro-4-methylphenyl)-1-(3-nitrophenyl)-2,4-dioxo-3-azabicyclo-[3.1.0]hexane-6-carboxylate as a mixture of *endo* (**IIIs**) and *exo* isomers (**IVs**) at a ratio of 1:1.8. Analogous reaction of spiro ester **IIf** afforded methyl 1-iodo-4,6-dioxo-5-(3,4-dichlorophenyl)-5-azaspiro-[2.4]heptane-1-carboxylate as a mixture of *syn* (**Vf**) and *anti* isomers (**VIf**) at a ratio of 1.2:1 (overall yield 55%). The structure of products **IIIs**/**IVs** and

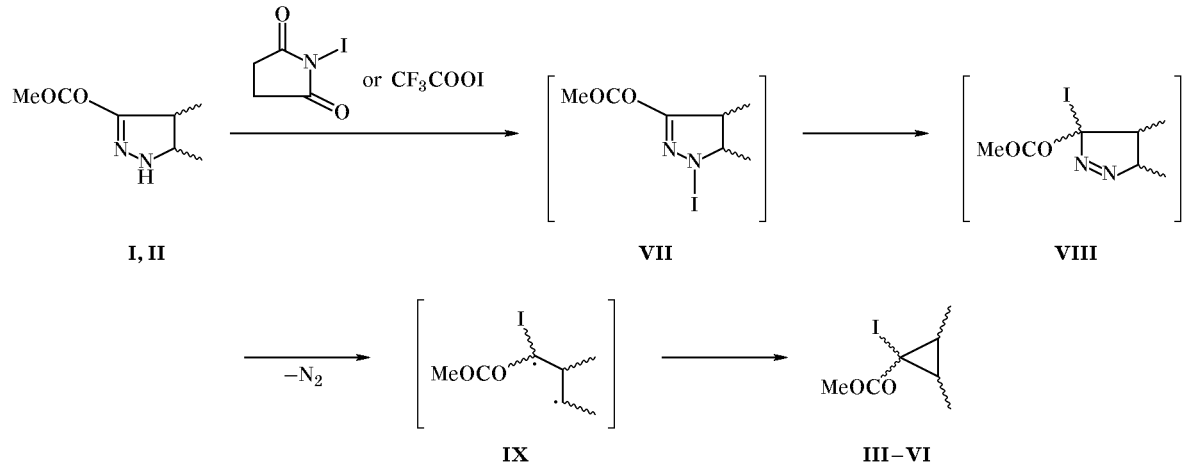
Scheme 3.



IIIs, IVs **Vf, VIf**

Is, **IIIs**, **IVs**, R = 3-$NO_2C_6H_4$, R′ = 3-Cl-4-MeC_6H_4; **IIf**, **Vf**, **VIf**, R = 3,4-$Cl_2C_6H_4$.

Scheme 4.



Vf/**VIf** was confirmed by elemental analyses (Table 1) and spectral data (Table 2).

Presumably, in the above reactions iodocyclopropanecarboxylates are formed by the same mechanism as that reported for their chloro-, bromo- [3, 4], and fluoro-substituted analogs [10]. Electrophilic iodination of pyrazoles **I** and **II** initially gives *N*-iodo derivatives **VII** which undergo rearrangement to 3-iodo-4,5-dihydro-3*H*-pyrazoles **VIII**. The latter lose nitrogen molecule, and cyclization of diradical species **IX** yields final cyclopropane compounds **III**–**VI** (Scheme 4). The stereoisomeric composition of the products is likely to be determined mainly by repulsion of the C–I and C=O dipoles which are arranged *cis* with respect to each other. As a result, *endo* isomers **IIIa**–**IIIc** and **VIa**–**VIe** are formed as the major products. When the *cis* position with respect to iodine is occupied by methyl or phenyl group, the formation of *endo* isomer becomes less favorable, and in these cases the corresponding *exo* isomer prevails in the product mixture (compounds **IVd**–**IVr**).

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer from 2% solutions in chloroform. The ^1H and ^{13}C NMR spectra were measured on a Bruker DPX-300 instrument at 300.13 and 75.47 MHz, respectively, using $CDCl_3$ as solvent. The reaction mixtures were analyzed, and the purity of products was checked, by TLC on Silufol UV-254 plates.

Methyl *endo*- and *exo*-6-iodo-2,4-dioxo-3-phenyl-3-azabicyclo[3.1.0]hexane-6-carboxylates (IIIa/IVa). A mixture of 0.21 g (0.8 mmol) of methyl 6,8-dioxo-7-phenyl-2,3,7-triazabicyclo[3.3.0]oct-3-ene-4-carboxylate (**Ia**) and 0.29 g (1.3 mmol) of *N*-iodosuccinimide in 10 ml of glacial acetic acid was heated for 1 h under reflux. The progress of the reaction was monitored by TLC. The solvent was distilled off, the residue was dissolved in an ether–ethyl acetate mixture, the solution was washed with a solution of sodium bisulfite, and the organic layer was separated and dried over magnesium sulfate. The solution was evaporated, and the residue was subjected to column chromatography on silica gel using hexane–ethyl acetate (1:1, by volume) as eluent. Yield of isomer mixture **IIIa**/**IVa** 0.073 g (26%). Esters **IIIb**/**IVb** and **IIIc**/**IVc** were synthesized in a similar way.

Methyl *endo*- and *exo*-6-iodo-1-methyl-2,4-dioxo-3-phenyl-3-azabicyclo[3.1.0]hexane-6-carboxylates (IIId/IVd). A mixture of 0.21 g (0.7 mmol) of methyl 1-methyl-6,8-dioxo-7-phenyl-2,3,7-triazabicyclo-[3.3.0]oct-3-ene-4-carboxylate (**Id**) and 0.23 g (1.0 mmol) of *N*-iodosuccinimide in 10 ml of glacial acetic acid was heated for 30 min at 80°C. The solvent was distilled off, the residue was dissolved in a mixture of ether with ethyl acetate, the solution was washed with a solution of sodium bisulfite, and the organic phase was separated and dried over magnesium sulfate. The solution was evaporated, and the residue was subjected to column chromatography on silica gel using hexane–ethyl acetate (2:1, by volume) as eluent. Yield of isomer mixture **IIId**/**IVd** 0.086 g (31%). Esters **IIIe**–**IIIr**/**IVe**–**IVr** were synthesized in a similar way.

Methyl *syn*- and *anti*-1-iodo-5-(3-chloro-4-methylphenyl)-4,6-dioxo-5-azaspiro[2.4]heptane-1-carboxylates (Vd/VId). A mixture of 0.4 g (1.4 mmol) of methyl 7-(3-chloro-4-methylphenyl)-6,8-dioxo-1,2,7-triazaspiro[4.4]non-2-ene-3-carboxylate (**IId**) and 0.47 g (2 mmol) of *N*-iodosuccin-

Table 2. IR and ^{1}H and ^{13}C NMR spectra of the newly synthesized compounds

Comp. no.	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm (*J*, Hz)	^{13}C NMR spectrum, δ_C, ppm
IIIa	890, 920, 990, 1070, 1260 s, 1380 s, 1440, 1500, 1600, 1720 v.s, 2950, 3080	3.12 s (2H), 3.88 s (3H), 7.37–7.49 (5H)	11.6, 34.2, 55.4, 126.5, 129.3, 129.6, 131.4, 166.1, 170.5
IIIb	920, 1050, 1260 s, 1380 s, 1480, 1500, 1610, 1720 v.s, 2840, 2960, 3050	3.10 s (2H), 3.83 s (3H), 3.86 c (3H), 6.92–7.36 (4H)	11.5, 34.1, 55.4, 55.9, 112.7, 114.9, 118.8, 130.3, 132.4, 160.4, 166.0, 168.5, 170.4
IIIc	920, 1020, 1080, 1100, 1260 s, 1380 s, 1490 s, 1720 v.s, 2960, 3050	3.13 s (2H), 3.85 s (3H), 7.35 d (2H, 9), 7.44 d (2H, 9)	11.3, 34.1, 55.5, 127.7, 129.7, 129.8, 135.1, 166.0, 170.2
IVd	900, 1080, 1140, 1280, 1380 s, 1450, 1510, 1600, 1720 v.s, 2950, 3050	1.61 s (3H), 3.20 s (1H), 3.87 s (3H), 7.40–7.50 (5H)	10.1, 15.4, 35.9, 38.6, 54.8, 126.5, 129.1, 129.5, 131.8, 165.8, 170.9, 173.8
IVe	900, 1140, 1280, 1380 s, 1460, 1520, 1720 v.s, 2960, 3050	1.60 s (3H), 2.39 s (3H), 3.19 s (1H), 3.87 s (3H), 7.28 s (4H)	10.2, 15.1, 21.8, 35.1, 38.6, 54.9, 126.4, 129.1, 130.1, 139.2, 165.7, 171.1, 173.8
IVf	900, 1020, 1100, 1140, 1280, 1380 s, 1490, 1720 v.s, 2960, 3050	1.61 s (3H), 3.21 s (1H), 3.88 s (3H), 7.37 d (2H, 9), 7.45 d (2H, 9)	10.0, 15.1, 35.9, 38.7, 54.8, 127.7, 129.7, 130.4, 134.9, 165.5, 170.8, 173.0
IVg	910, 1090, 1150, 1290, 1380 s, 1450, 1510, 1600, 1720 v.s, 2960, 3050	3.41 s (3H), 3.82 s (1H), 7.43–7.49 (10H)	17.0, 34.6, 46.1, 54.4, 126.6, 126.7, 129.0, 129.2, 129.5, 129.9, 130.1, 131.9, 164.3, 170.5, 171.1
IVh	910, 1090, 1160, 1290, 1380 s, 1450, 1520, 1720 v.s, 2960, 3050	2.40 s (3H), 3.41 s (3H), 3.81 (1H), 7.29–7.51 (9H)	17.0, 21.8, 34.6, 46.0, 54.5, 126.4, 126.9, 129.0, 129.8, 130.1, 139.5, 164.9, 170.5, 170.8
IVi	910, 1020, 1100, 1150, 1290, 1380 s, 1450, 1490 s, 1600, 1720, 2960, 3050	3.42 s (3H), 3.82 s (1H), 7.38–7.47 (9H)	16.9, 34.6, 46.0, 54.4, 126.6, 127.8, 129.1, 129.7, 129.9, 130.0, 130.1, 135.0, 164.4, 170.2, 170.8
IVj	910, 1090, 1120, 1160, 1290, 1380 s, 1440, 1520, 1600, 1720 v.s, 1960, 3050	2.37 s (3H), 3.44 s (3H), 3.79 s (1H), 7.21 d (2H, 8), 7.38 d (2H, 8), 7.39–7.47 (5H)	17.0, 21.8, 34.6, 45.9, 54.5, 123.8, 126.6, 129.2, 129.5, 129.8, 130.0, 131.7, 139.8, 164.8, 170.3, 171.0
IVk	910, 1090, 1120, 1160, 1290, 1380 s, 1440, 1520, 1600, 1720 v.s, 2960, 3050	2.37 s (3H), 2.39 s (3H), 3.43 s (3H), 3.77 s (1H), 7.21 d (2H, 8), 7.26 d (2H, 8), 7.32 d (2H, 8), 7.38 d (2H, 8)	17.0, 21.6, 21.7, 34.6, 45.8, 54.4, 123.5, 126.4, 129.0, 129.7, 129.9, 130.1, 138.8, 140.0, 164.5, 170.3, 171.2
IVl	910, 1020, 1100, 1160, 1290, 1380 s, 1520, 1720 v.s, 2960, 3050	2.37 s (3H), 3.44 s (3H), 3.78 s (1H), 7.22–7.40 (8H)	16.8, 21.6, 34.6, 45.9, 54.5, 123.7, 127.8, 129.7, 129.8, 129.9, 135.0, 139.8, 164.4, 170.2, 171.5
IVm	910, 1020, 1100, 1160, 1290, 1380 s, 1500, 1600, 1720 v.s, 2960, 3050	3.46 s (3H), 3.79 s (1H), 7.37–7.51 (9H)	16.7, 34.7, 45.4, 54.6, 125.2, 126.6, 129.3, 129.5, 131.5, 136.2, 164.4, 170.0, 170.5
IVn	910, 1020, 1100, 1160, 1290, 1380 s, 1520, 1600, 1720 v.s, 3050	2.40 s (3H), 3.46 s (3H), 3.78 s (1H), 7.25 s (4H), 7.38 d (2H, 8), 7.44 d (2H, 8)	16.8, 21.6, 34.7, 45.3, 54.5, 125.4, 126.4, 129.0, 129.3, 130.1, 131.5, 136.1, 139.4, 164.4, 170.5, 170.8

Table 2. (Contd.)

Comp. no.	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm (*J*, Hz)	^{13}C NMR spectrum, δ_C, ppm
IVo	910, 1020, 1100, 1160, 1280, 1380, 1590, 1720 v.s, 3050	3.47 s (3H), 3.79 s (1H), 7.36–7.47 (8H)	16.3, 34.8, 45.5, 54.8, 125.0, 127.7, 129.4, 129.7, 130.0, 131.5, 134.8, 136.2, 164.0, 169.8, 170.5
IVp	910, 1110, 1160, 1280, 1350 s, 1380, 1440, 1540, 1600, 1730 v.s, 2960, 3050	3.48 s (3H), 3.90 s (1H), 7.41–7.50 (5H), 7.63 t (1H, 8), 7.90 d (1H, 8), 8.31 d (1H, 8), 8.36 s (1H)	16.0, 35.0, 45.3, 54.8, 124.8, 125.2, 126.5, 129.2, 129.4, 129.7, 130.1, 131.2, 136.4, 148.8, 164.4, 169.5, 170.3
IVq	910, 1110, 1160, 1280, 1350 s, 1380, 1440, 1540, 1720 v.s, 2960, 3050	2.40 s (3H), 3.48 s (3H), 3.88 s (1H), 7.30 s (4H), 7.62 t (1H, 8), 7.90 d (1H, 8), 8.31 d (1H, 8), 8.36 s (1H)	16.1, 21.6, 35.0, 45.3, 54.7, 124.8, 125.1, 126.3, 128.7, 129.3, 130.1, 130.3, 136.4, 148.8, 164.3, 169.8, 170.5
IVr	910, 1100, 1160, 1280, 1350 s, 1490, 1540, 1720 v.s, 3030	3.48 s (3H), 3.90 s (1H), 7.38 d (2H, 8), 7.46 d (2H, 8), 7.63 t (1H, 8), 7.88 d (1H, 8), 8.28 d (1H, 8), 8.33 s (1H)	16.0, 35.0, 45.3, 54.8, 124.9, 125.1, 127.7, 128.7, 129.8, 130.2, 135.1, 136.4, 148.5, 164.2, 169.8, 170.2
IVs	920, 1060, 1110, 1160, 1280, 1350, 1380, 1450, 1500, 1540, 1720 v.s, 3050	2.39 s (3H), 3.46 s (3H), 3.89 s (1H), 7.21 m (1H), 7.30 m (1H), 7.42 m (1H), 7.61 t (1H, 8), 7.87 d (1H, 8), 8.28 d (1H, 8), 8.32 s (1H)	16.0, 20.3, 35.0, 45.3, 54.8, 124.7, 124.8, 125.1, 126.9, 129.1, 129.8, 129.9, 131.6, 135.0, 137.0, 137.7, 148.5, 164.2, 169.5, 170.2
VIa	870, 920, 970, 1100, 1170, 1280, 1390 s, 1510, 1720 v.s, 3050	1.64 d (1H, 7), 2.78 d (1H, 7), 2.98 d (1H, 19), 3.37 d (1H, 19), 3.78 s (3H), 7.28–7.51 (5H)	9.6, 30.3, 32.0, 40.8, 54.0, 126.7, 129.2, 129.6, 132.2, 168.0, 173.5, 173.9
VIb	870, 930, 970, 1050, 1100, 1160, 1280, 1390 s, 1520, 1720 v.s, 3050	1.63 d (1H, 7), 2.39 s (3H), 2.78 d (1H, 7), 2.97 d (1H, 19), 3.35 d (1H, 19), 3.77 s (3H), 7.17 d (2H, 8), 7.29 d (2H, 8)	9.6, 21.6, 30.1, 31.8, 40.7, 53.9, 126.5, 129.5, 130.2, 139.3, 168.0, 173.5, 174.0
VIc	920, 980, 1100, 1170, 1280, 1390 s, 1510, 1720 v.s, 3050	1.57 d (1H, 7), 2.27 s (6H), 2.70 d (1H, 7), 2.92 d (1H, 19), 3.29 d (1H, 19), 3.74 s (3H), 7.00 d (1H, 8), 7.03 s (1H), 7.21 d (1H, 8)	9.6, 20.0, 20.3, 30.1, 31.8, 40.8, 53.9, 124.2, 127.7, 129.7, 130.7, 138.1, 168.0, 173.6, 174.0
VId	970, 1060, 1100, 1160, 1280, 1390 s, 1500, 1720 v.s, 3050	1.63 d (1H, 7), 2.40 s (3H), 2.77 d (1H, 7), 2.97 d (1H, 19), 3.35 d(1H, 19), 3.77 s (3H), 7.11–7.38 (3H)	9.6, 20.3, 30.3, 31.8, 40.8, 54.0, 124.9, 127.2, 130.6, 131.6, 135.2, 137.5, 163.0, 173.1, 173.5
VIe	920, 970, 1020, 1080, 1100, 1160, 1280, 1390 s, 1490, 1720 v.s, 3050	1.65 d (1H, 7), 2.78 d (1H, 7), 2.98 d (1H, 19), 3.36 d (1H, 19), 3.78 s (3H), 7.22 d (2H, 8), 7.62 d (2H, 8)	9.8, 30.4, 31.8, 40.8, 54.0, 123.0, 128.2, 131.4, 132.8, 167.8, 173.1, 173.5
VIf	870, 970, 1030, 1090, 1160, 1280, 1380, 1480, 1720 v.s, 3050	1.63 d (1H, 7), 2.74 d (1H, 7), 2.97 d (1H, 19), 3.32 d (1H, 19), 3.75 s (3H), 7.23 m (1H), 7.43 m (1H), 7.52 m (1H)	9.5, 30.5, 31.8, 40.7, 54.0, 125.9, 128.5, 131.1, 131.3, 133.3, 167.8, 172.2, 173.0

imide in 10 ml of glacial acetic acid was heated for 25 min at 80°C. The solvent was distilled off, the residue was dissolved in ether, the solution was washed with a solution of sodium bisulfite, and the organic phase was separated and dried over magnesium sulfate. The solution was evaporated, and the residue was subjected to column chromatography on silica gel using hexane–ethyl acetate (2:1, by volume) as eluent. Yield of **Vd/VId** 0.3 g (56%). Esters **Va/VIa**, **Vb/VIb**, **Vc/VIc**, and **Ve/VIe** were synthesized in a similar way.

Methyl *endo*- and *exo*-6-iodo-3-(3-chloro-4-methylphenyl)-1-(3-nitrophenyl)-2,4-dioxo-3-azabicyclo[3.1.0]hexane-6-carboxylates (IIIs/IVs). A solution of 0.37 g (1.5 mmol) of iodine in 5 ml of 1,2-dichloroethane was added over a period of 10 min to a mixture of 0.433 g (1.0 mmol) of methyl 7-(3-chloro-4-methylphenyl)-1-(3-nitrophenyl)-6,8-dioxo-2,3,7-triazabicyclo[3.3.0]oct-3-ene-4-carboxylate (**Is**) and 0.73 g (2.8 mmol) of silver trifluoroacetate in 9 ml of 1,2-dichloroethane, stirred at 80°C. The mixture was stirred for 30 min at that temperature and cooled, and the precipitate of silver iodide was filtered off. The organic phase was washed with a 5% solution of sodium bisulfite, dried over magnesium sulfate, and evaporated, and the residue was subjected to column chromatography on silica gel using hexane–ethyl acetate (2:1, by volume) as eluent. Yield of isomer mixture **IIIs/IVs** 0.34 g (64%).

Methyl *syn*- and *anti*-1-iodo-5-(3,4-dichlorophenyl)-4,6-dioxo-5-azaspiro[2.4]heptane-1-carboxylates (Vf/VIf). A solution of 0.26 g (1.1 mmol) of iodine in 5 ml of 1,2-dichloroethane was added over a period of 10 min to a mixture of 0.24 g (0.7 mmol) of methyl 7-(3,4-dichlorophenyl)-6,8-dioxo-1,2,7-triazaspiro[4.4]non-2-ene-3-carboxylate (**IIf**) and 0.51 g (2.0 mmol) of silver trifluoroacetate in 7 ml of 1,2-dichloroethane, stirred at 80°C. The mixture was stirred for 40 min at that temperature and cooled, and the precipitate of silver iodide was filtered off. The filtrate was washed with a 5% solution of sodium bisulfite, dried over magnesium sulfate, and evaporated, and the residue was subjected to column chromatography on silica gel using hexane–ethyl acetate (2:1, by volume) as eluent. Yield of isomer mixture **Vf/VIf** 0.17 g (55%).

X-Ray analysis of compound IVh. $C_{20}H_{16}INO_4$, *M* 461.24, orthorhombic crystals, space group $P2_12_12_1$ (no. 19); unit cell parameters: a = 5.9827(4), b = 16.5754(12), c = 19.0061(13) Å; $\alpha = \beta = \gamma = 90.00°$; V = 1884.75(20) Å^3; Z = 4, d_{calc} = 1.625 g/cm^3; μ = 0.078 mm^{-1}, $F(000)$ = 912; MoK_a radiation, λ = 0.71073 Å, graphite monochromator. Below are given selected bond lengths (Å) and bond angles (deg): $I^{61}-C^6$ 2.132(3), N^3-C^4 1.395(4), N^3-C^2 1.401(3), N^3-C^{31} 1.443(3), C^1-C^5 1.508(4), C^1-C^2 1.520(4), C^1-C^6 1.527(4), C^4-C^5 1.509(4), C^5-C^6 1.507(4), $C^4N^3C^2$ 113.06(24), $C^5C^1C^2$ 105.34(23), $C^5C^1C^6$ 59.51(18), $C^2C^1C^6$ 115.37(22), $N^3C^2C^1$ 107.52(20), $N^3C^4C^5$ 107.59(22), $C^6C^5C^1$ 60.87(19), $C^6C^5C^4$ 115.19(23), $C^1C^5C^4$ 106.21(22), $C^5C^6I^{61}$ 121.45(19). The complete set of crystallographic parameters was included into the Cambridge Structural Database.

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