New Compounds in Ring-opening Reaction of 5-Substituted Epoxyisoindolines

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Methoxy or nitro group present in the furan ring of tertiary alkenylfurfurylamine changes the expected results of both, the intramolecular [4+2]cycloaddition and the acid catalyzed ring-opening reaction of the derived oxatricycloadduct. With a 5-methoxy group, in addition to the expected 5-methoxyisoindoline **3**, the corresponding hydroxy derivative **5** was obtained. On the other hand a 5-nitro group changes the outcome of the reaction even more profoundly. Instead of the expected 5-nitroisoindoline **12**, 5-nitro-substituted epoxyisoindoline **6** submitted to ring-opening reaction with the mixture of hydrobromic and acetic acid, yielded the mixture of bromo-substituted epoxy compounds **7, 8**, **9** and/or bromo-substituted isoindolines **10** and **11**.

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The intramolecular Diels-Alder reaction (IMDA reaction) has proved over the years to be the most versatile key step in the synthesis of condensed carbo- or heterocyclic systems and has been included in many natural product syntheses. In spite of the fact that examples of intramolecular Diels-Alder reactions with a furan nucleus as the dienic component (IMDAF reaction [1]) are less numerous, a number of papers have appeared in recent years illustrating its scope and usefulness in many syntheses [2].

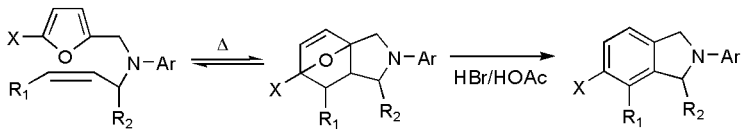
Recently we suggested a useful procedure to convert simple furans to substituted isoindolines *via* epoxyisoindolines (Scheme 1) [3]. The process includes the intramolecular Diels-Alder reaction of tertiary *N*-alkenyl-*N*-aryl-2-furfurylamine [4] and subsequent aromatization of the formed oxatricycloadduct through the ring-opening reaction [5] by hydrobromic acid in glacial acetic acid.

The early example of intramolecular [4+2]cycloaddition with simple furans, that is *N*-alkenyl-*N*-aryl-*N*-(2-furfuryl)amines, was reported from our laboratory more than three decades ago [6a]. Since that time the IMDAF reaction has been used by us [3,4,7] and others [8] as a simple synthetic step towards nitrogen containing heterocycles and for studies of substituent effects in cyclization reactions. Further reactions which include the epoxy- bridge of IMDAF adducts may lead to sometimes rare heterocycles or natural products difficult to approach by other procedures.

The ring-opening reaction of substituted oxatricycloadduct (epoxyisoindoline), in acidic media is usually straightforward [5], but the process is dependant on substituents [3], leading to the corresponding isoindoline. Unexpectedly, during a study of the substituent influence on the reaction we found a bridgehead methoxy or nitro substituents to generate a specific outcome.

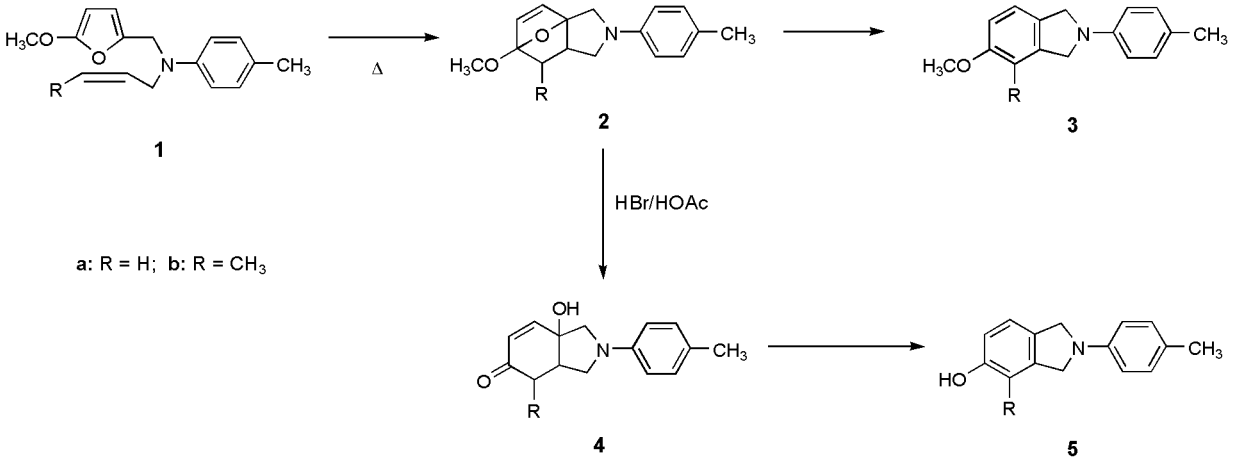
Regarding 5-methoxy derivatives, we found profound enhancement of the spontaneous ring-opening reaction of oxatricycloadducts [9] which prevented the isolation of epoxyisoindolines **2** [3,4]. The isolation of the crude reaction product containing the majority of 5-methoxyisoindo-

Scheme 1



X = H, CH_3, OCH_3, NO_2, I; R_1 = H, CH_3; R_1,R_2 = -$(CH_2)_3$-; Ar = *p*-$CH_3C_6H_4$

Scheme 2



line **3b** (R = CH_3) and a small amount of hydroxyenone **4b** [7e], prompted us to study these transformations (Scheme 2) more closely. Obviously, the presence of a 5-methoxy group in *N*-alkenyl-*N*-furfuryl-*N*-arylamine improves not only the reactivity in the sense of IMDAF reaction but even more, the susceptibility to ring-opening reaction for the formed oxatricycloadduct. Both, **1a** (R = H) and **1b** (R = CH_3) subjected to IMDAF reaction produce epoxyisoindolines **2a** and **2b** [4] but only **2a** was possible to isolate and purify by crystallization of the crude product. The presence of 4-methyl group in **1b** both activates the molecule and, with formation of **2b**, drives the spontaneous aromatization *via* ring-opening reaction of the epoxy-bridge. This aromatization prevented the isolation of **2b** [10]. The reaction conditions applied, allowed in fact two kinds of epoxyisoindoline ring openings. Beside the dominant, above mentioned, aromatization **2b**→**3b**, the transformation **2b**→**4b** took place as well (Scheme 2). It is proposed that both reactions are initiated by traces of atmospheric moisture attacking the epoxy-bridge in **2b** as soon as it was formed by the IMDAF reaction of **1b**. As a consequence, the reaction product is comprised of **3b** and **4b** (10:1 respectively). Since we believed that hydroxyisoindolone may be the intermediate in the aromatization of **2** to **5** we found essential within the present study to prepare **4** for the full characterization.

The similar set of reactions was carried out with **2a** to prove the outcome and allow further conclusions about the influence of a 4-methyl substituent to studied reactions. The ring-opening reaction of pure oxatricycloadduct **2a**, isolated by the crystallization of crude IMDAF adduct was performed by heating of their chloroform solution in the presence of silica gel yielding exclusively **4a** (92%). Under the same reaction conditions but with alumina instead of silica gel, the mixture of **3a** (70%) and **4a** (15%) was obtained. Separated hydroxyenone **4a** was successfully aromatized by heating of the solution in the mixture of hydrobromic and acetic acid, with the yield comparable to those reported for direct reaction of **2a** to **5a** [3]. Hydroxyenones **4a** and **4b** obtained during the present reinvestigation were duly characterized by elemental analyses, ir, nmr and mass spectra.

Additionally, a single crystal X-ray diffraction confirmed the structure of **4a**. The crystallographic data, final atomic coordinates for non-hydrogen atoms and bond distances and angles are summarized in Tables 1-3. The ORTEP view of **4a** made by the PLATON98 program [11] is shown in Figure 1.

Table 1

General and Crystal Data and Summary of Intensity Data Collection and Structure Refinement of **4a**

Formula	$C_{15}H_{16}NO_2$
M_r	243.30
Color and habit	Colorless, Plate
Crystal system, Space group	Monoclinic, $P\ 2_1/c$
Crystal dimensions (mm^3)	$0.23 \times 0.17 \times 0.06$
Unit cell parameters:	
a (Å)	10.482(5)
b (Å)	10.892(5)
c (Å)	11.491(5)
β (°)	101.44(2)
V ($Å^3$)	1285.9(10)
Z	4
D_c (gcm^{-3})	1.257
μ (mm^{-1})	0.083
F(000)	520
Temperature (K)	293
Diffractometer	Philips PW 1100 updated by STOE
Radiation: MoK_α, λ (Å)	0.71073
2θ range for data collection (°)	4 - 54
h, k, l range	-13 to 13, 0 to 13, 0 to 14
Scan type	ω
No. measured reflections	2942
No. independent reflections	2802 (R_{int}) = 0.0783
No. refined parameters	165
No. observed reflections, $I \geq 2\sigma(I)$	555
R [a], wR [$I \geq 2\sigma(I)$]	0.0471, 0.1079
R, wR [b] [all data]	0.2910, 0.1589

Table 1 (continued)

Goodness of fit on F^2, S [c]	0.62
g_1, g^2 in w [d]	0.0810, 0
Max., min. electron density (e Å^{-3})	0.21; -0.21
Maximum Δ/σ	<0.001

[a] $R = \Sigma \| |F_o| - |F_c| | / \Sigma |F_o|$; [b] $wR = [\Sigma(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$; [c] $S = \Sigma[w(F_o^2 - F_c^2)^2/(N_{obs} - N_{param})]^{1/2}$; [d] $w = 1/[\sigma^2(F_o^2) + g_1P + g_2P]$ where $P = (F_o^2 + 2F_c^2)/3$.

Table 2

Atomic Coordinates and Equivalent Isotropic Displacement Parameters (Å^2) for **4a**

Atom	*x*	*y*	*z*	*Ueq* [a]
O1	-0.3727(3)	0.2297(3)	-0.0758(3)	0.0640(11)
O2	-0.5658(3)	-0.0328(3)	-0.3310(3)	0.0810(14)
N	-0.1262(3)	0.1292(3)	0.0413(3)	0.0539(16)
C1	-0.1417(3)	0.2045(4)	-0.0651(3)	0.0493(17)
C2	-0.2774(4)	0.1693(4)	-0.1316(3)	0.0405(16)
C3	-0.3133(4)	0.1864(4)	-0.2618(3)	0.0499(17)
C4	-0.4036(4)	0.1158(4)	-0.3262(3)	0.0559(19)
C5	-0.4688(4)	0.0176(4)	-0.2734(4)	0.0528(17)
C6	-0.4187(4)	-0.0161(4)	-0.1456(3)	0.0546(17)
C7	-0.2822(3)	0.0343(4)	-0.1011(3)	0.0400(16)
C8	-0.2206(3)	0.0286(4)	0.0304(3)	0.0447(16)
C9	-0.0258(4)	0.1440(4)	0.1366(3)	0.0429(16)
C10	-0.0128(4)	0.0686(4)	0.2371(4)	0.0473(16)
C11	0.0901(4)	0.0822(4)	0.3327(3)	0.0538(19)
C12	0.1842(4)	0.1725(4)	0.3353(4)	0.0475(17)
C13	0.1712(3)	0.2480(4)	0.2370(4)	0.0498(16)
C14	0.0691(3)	0.2360(4)	0.1410(4)	0.0475(16)
C15	0.2977(4)	0.1859(4)	0.4398(3)	0.0713(19)

[a] *Ueq* is the one third of the trace of the orthogonalized U tensor.

Table 3

Bond Lengths (Å) and Bond Angles (°) for **4a**

Bond lengths

O1-C2	1.448(5)	C5-C6	1.504(6)
O2-C5	1.227(5)	C6-C7	1.523(5)
N-C8	1.465(5)	C7-C8	1.522(5)
N-C9	1.370(5)	C9-C10	1.402(6)
N-C1	1.454(5)	C9-C14	1.406(6)
C1-C2	1.524(5)	C10-C11	1.386(6)
C2-C3	1.480(5)	C11-C12	1.389(6)
C2-C7	1.515(6)	C12-C13	1.382(6)
C3-C4	1.326(6)	C13-C14	1.382(6)
C4-C5	1.464(6)	C12-C15	1.521(6)

Bond angles

C1-N-C9	123.1(3)	C5-C6-C7	111.3(3)
C8-N-C9	123.7(3)	C2-C7-C8	104.0(3)
C1-N-C8	112.9(3)	C6-C7-C8	120.3(3)
N-C1-C2	102.5(3)	C2-C7-C6	110.1(3)
O1-C2-C1	108.7(3)	N-C8-C7	101.6(3)
O1-C2-C7	106.3(3)	N-C9-C14	122.6(4)
C1-C2-C3	120.0(3)	C10-C9-C14	115.8(4)
O1-C2-C3	109.3(3)	N-C9-C10	121.6(4)
C3-C2-C7	110.0(3)	C9-C10-C11	121.6(4)
C1-C2-C7	101.5(3)	C10-C11-C12	122.0(4)
C2-C3-C4	120.1(4)	C11-C12-C13	116.7(4)
C3-C4-C5	122.2(3)	C11-C12-C15	121.7(4)
O2-C5-C6	120.6(4)	C13-C12- C15	121.6(4)
C4-C5-C6	118.8(4)	C12-C13- C14	122.1(4)
O2-C5-C4	120.5(4)	C9-C14-C13	121.8(4)

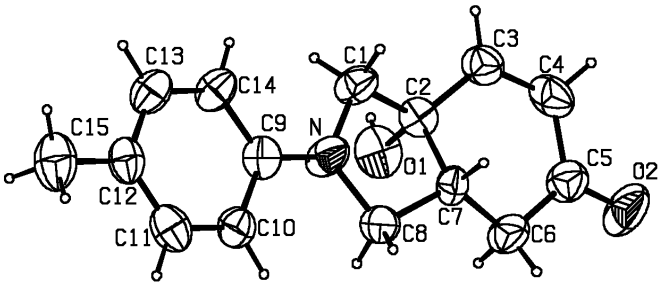


Figure 1. A perspective view and atom labeling scheme for the molecular structure of **4a**.

Quite different behavior was observed with the electron withdrawing nitro group. The influence of bridgehead nitro group in oxatricycloadducts retarded the reaction with hydrobromic acid/acetic acid reagent so efficiently that aromatization was detected only if the additional electrondonor (4-methyl group in **6**) was present. Although the aromatization was operable, the expected *N*-(4-methylphenyl)-4-methyl-5-nitroisoindoline (**12**) was not

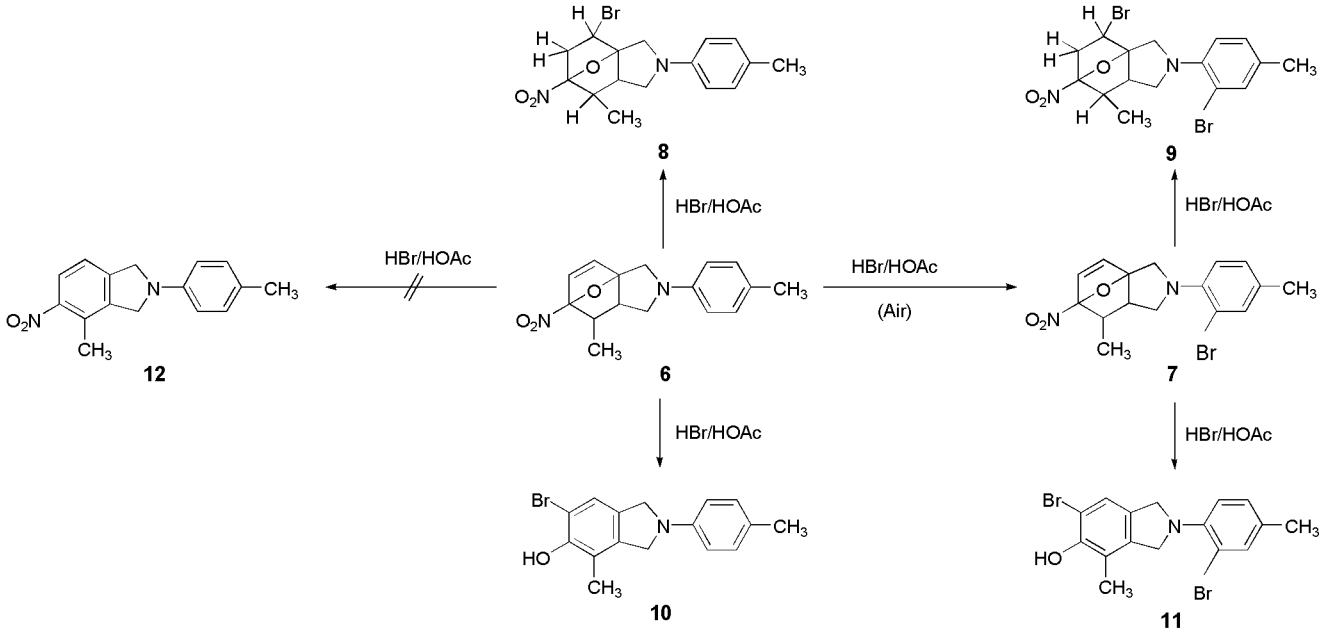
Table 4

General and Crystal Data and Summary of Intensity Data Collection and Structure Refinement of **11**

Formula	$C_{16}H_{15}Br_2NO$
M_r	397.09
Color and habit	Colorless needle
Crystal system, Space group	Monoclinic, $P\,2_1/a$ (No. 14)
Crystal dimensions (mm^3)	0.4 × 0.08 × 0.1
Unit cell parameters:	
a (Å)	15.4750(5)
b (Å)	4.5060(5)
c (Å)	21.2270(5)
β (°)	99.050(2)
V (Å^3)	1461.74(17)
Z	4
D_c (gcm^{-3})	1.804
μ (mm^{-1})	5.5
$F(000)$	784
Temperature (K)	200
Diffractometer	KappaCCD Nonius
Radiation: MoK$_\alpha$, λ (Å)	0.71073
2θ range for data collection (°)	4 - 54
h, k, l range	-19 to 20, -5 to 5, -27 to 27
Scan type	ω
No. measured reflections	9196
No. independent reflections	3310 (R_{int})=0.090
No. refined parameters	182
No. observed reflections, $I \geq 2\sigma(I)$	1947
R [a], wR [$I \geq 2\sigma(I)$]	0.068, 0.113
R, wR [b] [all data]	0.137, 0.134
Goodness of fit on F^2, S [c]	1.14
g_1, g^2 in w [d]	0.0218, 3.4744
Max., min. electron density (e Å^{-3})	0.40; -0.37
Maximum Δ/σ	<0.001

[a] $R = \Sigma \| |F_o| - |F_c| | / \Sigma |F_o|$ [b] $wR = [\Sigma(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$; [c] $S = \Sigma[w(F_o^2 - F_c^2)^2/(N_{obs} - N_{param})]^{1/2}$; [d] $w = 1/[\sigma^2(F_o^2) + [g_1P + g_2P]$ where $P = (F_o^2 + 2F_c^2)/3$.

Scheme 3



detected. Instead, under the applied reaction condition monobromo- and/or dibromoisoindolines **10** and **11** were isolated. Besides, by the modification of reaction conditions (surplus of the reagent, temperature and reaction time) small quantities of bromo substituted epoxy-compounds **7**, **8** and **9** were also separated (Scheme 3).

Table 5

Atomic Coordinates and Equivalent Isotropic Displacement Parameters (Å^2) for **11**

Atom	*x*	*y*	*z*	*Ueq* [a]
Br1	0.33597(4)	0.16328(15)	0.38249(3)	0.0598(3)
Br2	0.08515(5)	1.1323(2)	0.08375(4)	0.0840(3)
O	0.2034(3)	0.3944(9)	0.46570(19)	0.0525(17)
N	0.0419(3)	1.0173(12)	0.2319(2)	0.0495(17)
C1	0.1180(4)	0.8495(14)	0.2190(3)	0.051(2)
C2	0.1485(4)	0.7018(13)	0.2809(3)	0.0444(19)
C3	0.2191(4)	0.5146(13)	0.2966(3)	0.048(2)
C4	0.2375(4)	0.4119(12)	0.3580(3)	0.0443(19)
C5	0.1863(4)	0.4898(13)	0.4041(3)	0.045(2)
C6	0.1150(4)	0.6746(13)	0.3887(3)	0.0431(17)
C7	0.0979(4)	0.7792(13)	0.3264(3)	0.0451(17)
C8	0.0262(4)	0.9779(14)	0.2973(3)	0.048(2)
C9	-0.0134(4)	1.1959(13)	0.1899(3)	0.048(2)
C10	-0.0067(4)	1.2677(14)	0.1270(3)	0.051(2)
C11	-0.0663(4)	1.4489(14)	0.0903(3)	0.055(2)
C12	-0.1345(4)	1.5781(13)	0.1130(3)	0.052(2)
C13	-0.1429(4)	1.5122(14)	0.1756(3)	0.054(2)
C14	-0.0843(4)	1.3278(14)	0.2127(3)	0.052(2)
C15	-0.1995(4)	1.7762(15)	0.0729(4)	0.065(3)
C16	0.0569(4)	0.7592(15)	0.4365(3)	0.062(3)

[a] *Ueq* is the one third of the trace of the orthogonalized U tensor.

The presence of the compound **8** could be explained by the addition of hydrogen bromide to the epoxyisoindoline

Table 6

Bond Lengths (Å) and Bond Angles (°) for **11**

Bond lengths

Br1-C4	1.897(6)	C4-C5	1.397(9)
Br2-C10	1.909(6)	C5-C6	1.380(9)
O-C5	1.362(7)	C6-C16	1.507(9)
C13-C14	1.381(9)	C6-C7	1.390(9)
N-C1	1.461(8)	C7-C8	1.483(9)
N-C9	1.391(8)	C9-C14	1.399(9)
N-C8	1.457(8)	C9-C10	1.393(9)
C1-C2	1.482(9)	C10-C11	1.378(9)
C2-C7	1.380(9)	C11-C12	1.358(9)
C2-C3	1.379(9)	C12-C15	1.505(9)
C3-C4	1.370(9)	C12-C13	1.387(9)

Bond angles

C9-N-C1	127.7(5)	C2-C7-C6	122.5(6)
C9-N-C8	120.2(5)	C2-C7-C8	109.2(5)
C1-N-C8	112.1(5)	C6-C7-C8	128.3(5)
N-C1-C2	102.7(5)	N-C8-C7	104.2(5)
C3-C2-C7	120.0(5)	C10-C9-N	128.1(5)
C3-C2-C1	128.2(5)	C10-C9-C14	114.4(6)
C7-C2-C1	111.8(5)	N-C9-C14	117.5(5)
C4-C3-C2	118.3(5)	C11-C10-C9	122.4(6)
C3-C4-C5	121.7(5)	C11-C10-Br2	113.5(5)
C3-C4-Br1	119.8(4)	C9-C10-Br2	124.0(5)
C5-C4-Br1	118.5(5)	C12-C11-C10	122.8(6)
O-C5-C6	116.3(5)	C11-C12-C13	116.3(6)
O-C5-C4	123.2(5)	C11-C12-C15	122.8(6)
C6-C5-C4	120.5(5)	C13-C12-C15	120.9(6)
C5-C6-C7	117.1(5)	C14-C13-C12	121.5(6)
C5-C6-C16	122.2(5)	C13-C14-C9	122.7(6)
C7-C6-C16	120.7(6)		

double bond of **6**. The 7-bromo-compound **8** were isolated without any sign of aromatization. Similarly, the formation of *N*-(2-bromo-4-methylphenyl) derivative **9** could be explained by the intermediate formation of *N*-(2-bromo-4-methylphenyl)-4-methyl-5-nitro-3a,4,5,7a-tetrahydro-5,7a-epoxyisoindoline (**7**) *via o*-bromination of the *N*-aryl group in **6** [12], followed by the addition of hydrogen bromide to epoxyisoindoline double bond. The 7-bromo derivative **9** was isolated, like with compound **8**, without any sign of aromatization.

The obtained bromo-compounds **10** and **11** were fully characterized by elemental analyses, ir, nmr and mass spectra. Additionally, the structure of **11** was confirmed by X-ray crystallographic measurement. The crystallographic data, final atomic coordinates for non-hydrogen atoms and bond distances and angles are summarized in Tables 4-6. The ORTEP drawing of **11** is depicted in Figure 2.

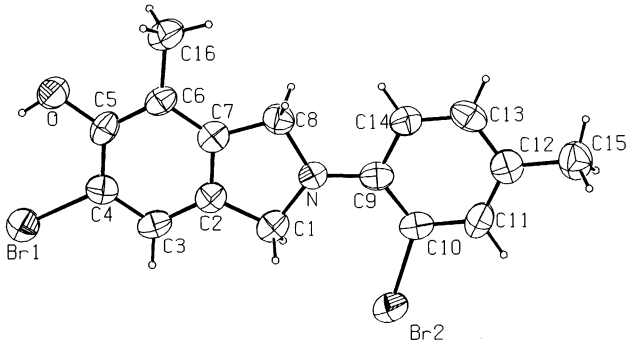
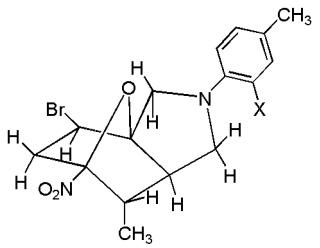


Figure 2. A perspective view and atom labeling scheme for the molecular structure of **11**.

To explain the presence of the undoubtedly confirmed 5-hydroxy group in **10** and **11** we tentatively suggest the ring-opening reaction under nucleophylic attack at C7a [3,5], with formation of the corresponding very unstable geminal hydroxy-nitro intermediate, which possibly could lead to aromatized compounds **10** and **11**. On the other hand, the attack at C7a and the ring-opening reaction, in case of saturated 7-bromo epoxy-compounds **8** and **9** must be more or less suppressed by the vicinity of bromine, preventing the expected aromatization and making possible the isolation of the corresponding 5-nitro-hexahydroepoxyisoindoline.

The structure determination of hexahydroepoxyisoindolines **8** and **9**, especially regarding the position of the bromine, rests mostly on an elaborate spectroscopic analysis (ir, ^{1}H, ^{13}C nmr and mass spectra). The proton-proton and proton-carbon correlation found within ^{1}H and ^{13}C nmr spectra using additional techniques (NOESY, COSY and HMBC) allow us to select the most probable structures (Figure 3).



8 (X = H), **9** (X = Br)

Figure 3. *N*-Aryl-7-bromo-4-methyl-5-nitro-3a,4,5,6,7,7a-hexahydro-5,7a-epoxy-isoindolines **8** and **9**.

Perhaps the most compelling resonance assignment in compound **8** is that of the resonance of the proton C7-H at 4.35 ppm, which is well within the normal range for the hydrogen at this position (at bromine bearing C-atom). The HMBC spectra shows the correlation with carbon 3a-C at 52.6 ppm and the correlation with the nitrogen bearing carbon 5-C at 112.4 ppm both of which are three-bond ($^{3}J_{CH}$) correlations (Figure 4).

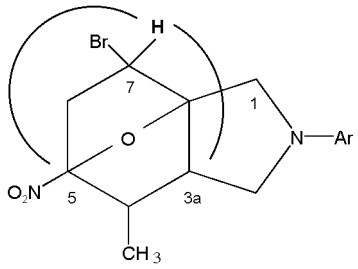


Figure 4. Selected HMBC correlation in compound **8** and **9.**

The similarity of HMBC spectral data of **9**, showing the $^{3}J_{CH}$ correlation between proton C7-H at 4.85 ppm with carbons 3a-C and 5-C at 52.5 and 113.0 ppm approved the analogy of structures **8** and **9** (Figure 4).

The NOESY spectra indicate the *exo*-oriented bromine, which allowed the possibility of a through-space interaction of protons C7-H and C3a-H. The other two- and three-bond correlation in HMBC spectra of the two 7-bromo compounds are in full agreement with the proposed structure.

The structure of aromatized product **10** was deducted from its full spectroscopic assignments (ir, ^{1}H, ^{13}C nmr and mass spectra) including NOE correlation. The balances of the long-range heteronuclear correlation in the HMBC spectrum were fully consistent with the proposed structure (Figure 5).

The question on the location of the bromine atom at 6-C in compound **10** with proton C7-H at 7.22 ppm was resolved from the long range ^{1}H-^{13}C correlation. The pro-

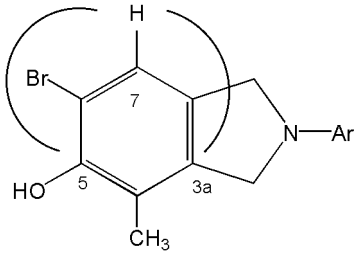


Figure 5. Selected HMBC correlation in compound **10**.

ton C7-H couples with carbons 3a-C at 138.7 ppm and 5-C at 149.2 ppm *via* $^3J_{CH}$. The eventually supposed correlation of the proton C6-H for 7-bromo substituted analogue *via* $^4J_{CH}$ to 3a-C should be considerably less reasonable.

The structure of *N*-(2-bromo-4-methylphenyl)-6-bromo-5-hydroxyisoindoline (**11**) was similarly deducted from its full spectroscopic assignments (ir, ^{1}H, ^{13}C nmr and mass spectra) and was confirmed by X-ray structure determination..

EXPERIMENTAL

Melting points were determined on an "Original Kofler Mikroheitztisch" apparatus (Reichardt, Wien) and are not corrected. Infrared spectra were taken in potassium bromide pellets with a Perkin-Elmer Model 297 instrument. The proton nmr spectra were obtained using a Varian GEMINI 300 spectrometer, a Brucker AVANCE DPX 300 or a Brucker AVANCE DRX 500 nmr spectrometer (working at 500.13 MHz) with tetramethylsilane as the internal standard. The ^{13}Carbon nmr spectra were recorded on a Varian GEMINI 300 instrument at 75 MHz using the APT technique and a BRUCKER AVANCE DPX 300 or a Brucker AVANCE DRX 500 nmr spectrometer (working at 125.77 MHz). Mass spectra were recorded on the Extrel FTMS 2001 DD spectrometer by a direct insertion probe using electron impact or N_2 laser ionization. The molecular structure was determined by X-ray diffraction using the Philips PW 1100 or the KappaCCD Nonius diffractometer.

N-(4-Methylphenyl)-7a-hydroxy-3a,4,5,7a-tetrahydroisoindolin-5-one (**4a**).

Procedure A.

Silica gel (4.0 g, chromatographic grade) was added to the solution of 129 mg (5 mmol) of *N*-(4-methylphenyl)-5-methoxy-5,7a-epoxy-3a,4,5,7a-tetrahydroisoindoline (**2a**) [7b] in 10 ml of chloroform. The reaction mixture was heated under reflux for 3 hours. Silica gel was removed by filtration and the solvent evaporated. Crude crystalline **4a** (93.8 mg, 92%) melted at 205-206 °C.

Procedure B.

From **2a** by the reaction procedure as mentioned above, only with neutral aluminum oxide (Grade I) instead of silicagel. *N*-(4-Methylphenyl)-7a-hydroxy-3a,4,5,7a-tetrahydroisoindolin-5-one (**4a**) was obtained as colorless crystals, yield 15%, mp 206-207 °C [14]; ir (potassium bromide): 3480bs (OH), 1675s (C=O), 1620s (C=C) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.94 (s, 1H, D_2O exchangeable) for C7a-OH group, 7.22 (d, 1H, J = 9.8 Hz) and 6.10 (d, 1H, J = 9.8 Hz) for enone C7-H and C6-H respectively, 3.52 (d, 1H, J = 10.0 Hz) and 3.46 (d, 1H, J = 10.0 Hz) for protons at C1, 3.51 (t, 1H, J = 9.6) and 3.34 (t, 1H, J = 9.6 Hz) for protons at C3, 2.65 (d, 1H, J = 17.2 Hz for C3a-H, 2.61 (d, 1H, J = 17.2 Hz) and 2.87 (dd, 1H, J = 17.2 Hz, J' = 4.0 Hz) for protons at C4, 7.07 (d, 2H, J_{A2X2} = 8.5 Hz) and 6.49 (d, 2H, J_{A2X2} = 8.5 Hz) for p-phenylene protons at C3,3' and C2,6' respectively, 2.26 ppm (s, 3H) for p-CH_3; ^{13}C nmr (deuteriochloroform): δ 145.4 (d) and 132.0 (d) for unsaturated isoindolone carbons 7-C and 6-C respectively, 198.7 (s) for carbonyl 5-C; 57.5 (t), 49.5 (t), 44.0 (d), 35.7 (t) and 72.9 (s) for saturated isoindolone carbons 1-C, 3-C, 3a-C, 4-C and 7a-C respectively, 145.2 (s), 111.3 (d), 129.6 (d) and 125.5 (s) for p-phenylene ring carbons 1'-C, 2'-C, 3'-C and 4'-C respectively, 20.0 ppm (q) for p-CH_3; ms (EI, 10 eV): m/z (relative intensity) 244 (20, $[M+H]^+$), 243 (100, M^+), 134 (15), 133 (95), 120 (10), 105 (45), 91 (5); hrms: $[M^+]$ calc'd for $C_{15}H_{17}NO_2$: 243.12593; found: 243.11283.

Anal. Calc'd. for $C_{15}H_{17}NO_2$ (M_r=243.30): C 74.05, H 7.04, N 5.76%; found: C 74.19, H 7.07, N 5.78%.

Single Crystal X-ray Structural Determination of **4a**.

Colorless monoclinic crystals in a form of thin plates were obtained by repeated recrystallization from acetone/water 5:2. Suitable crystals were formed on very slow crystallization during 5 days at –3 °C. Data collection was carried out on a four-circle automatic PW 1100 diffractometer. The program STADI4 [15] was used for data collection and the program X-RED for data reduction [16]. The structure was determined by the program DIRDIF-96 [17] by fitting of known structural fragment of pronounced rigidity *i.e. N*-p-tolyl moiety, on the basis of vector search methods. The initial chemically reasonable isotropic model was further refined by using SHELXL97 program [18]. All non-hydrogen atoms were refined anisotropically based on F^2 by full-matrix least-squares method. All hydrogen atoms were included in calculated positions as riding atoms with the SHELXL97 [18] default parameters.

N-(4-Methylphenyl)-7a-hydroxy-4-methyl-3a,4,5,7a-tetrahydroisoindolin-5-one (**4b**).

The tertiary amine **1b** (1.36 g, 5 mmol) dissolved in dried benzene was heated for 48 hours at 50 °C. The formation of **2b** was indicated by ^{1}H nmr spectra in the experiment carried out in deuteriochloroform solution of **1b** standing at –18 °C for several months. The compound **2b** was not isolated due to the spontaneous aromatization to **3b** [7e]. After evaporation, the crude product was purified by a column chromatography on neutral aluminum oxide with hexane/chloroform 5:1 and hexane/ether 10:1. After the separation of **3b** (75%) and a small amount of starting compound, pure crystalline hydroxyenone **4b** (0.9 g, 7%) melting at 164-165 °C was obtained; ir (potassium bromide): ν 3500s (OH), 2920m, 2840w, 1675s (C=O), 1620m (C=C), 1525vs, 1380m, 920m, 800s cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.03 (s, 1H, D_2O exchangeable) for C7a-OH group, 7.15 (d, 1H, J = 9.8 Hz) and 6.08 (d, 1H, J = 9.8 Hz) for enone C7-H and C6-H respectively, 3.52 (d, 1H, J = 10.0 Hz) and 3.46 (d, 1H, J = 10.0 Hz) for protons at C1, 3.40 (t, 1H, J = 9.0) and 3.37 (t, 1H, J = 9.0 Hz) for protons at C3, 2.97-2.86 (m, 1H) for C4-H; 1.21 (d, 3H, J = 6.9 Hz) for isoindolinone C4-CH_3, 2.40-2.30 (m, 1H) for C3a-H, 7.15 (d, 2H, J_{A2X2} = 8.0 Hz) and 6.50 (d, 2H, J_{A2X2} = 8.0 Hz) for p-phenylene protons at

C3,5' and C2,6' respectively, 2.26 ppm (s, 3H) for p-CH_3; ^{13}C nmr (deuteriochloroform): δ 144.4 (d) and 132.1 (d) for unsaturated isoindolinone 7-C and 6-C respectively, 201.5 (s) for carbonyl 5-C, 57.8 (t), 48.9 (t), 50.4 (d), 40.1 (d) and 73.5 (s) for saturated isoindolinone 1-C, 3-C, 3a-C, 4-C and 7a-C respectively, 12.5 (q) for methyl at 4-C, 145.4 (s), 111.5 (d), 129.8 (d) and 125.7 (s) for p-phenylene carbons 1'-C, 2'-C, 3'-C and 4'-C respectively, 20.0 ppm (q) for p-CH_3; ms (EI, 10 eV): m/z (relative intensity) 258 (30, $[M+H]^+$), 257 (100, M^+), 224 (45), 196 (5), 149 (5), 134 (10), 133 (45), 120 (10), 105 (40); hrms: $[M^+]$ calc'd for $C_{16}H_{19}NO_2$: 257.14158; found: 257.14103.

Anal. Calc'd. for $C_{16}H_{19}NO_2$ (M_r=257.33): C 74.68, H 7.44, N 5.44%; found: C 74.56, H 7.47, N 5.55%.

N-(4-Methylphenyl)-5-hydroxyisoindoline (**5a**).

The Preparation from Isolated **4a**.

The solution of hydroxyenone **4a** (49 mg, 2 mmoles) in a mixture of glacial acetic and 48% hydrobromic acid (1:1) was heated at 60 °C for 3 days under protection from light. The reaction mixture was poured into ice-cold water and carefully neutralized with 5% sodium hydroxide solution (pH 6-7). The solution was extracted with diethyl ether. From the dried etheral solution **5a** was isolated on a silica gel column protected from light, using petroleumether/ether 5:1 as eluent. Colorless crystals (43 mg, 95%) melting at 159-160 °C proved to be identical with the original sample [3] by the comparison of their elemental analysis, ir, nmr and mass spectra.

Reaction of *N*-(4-Methylphenyl)-4-methyl-5-nitro-3a,4,5,7a-tetrahydro-5,7a-epoxyisoindoline (**6**) with Hydrobromic Acid/Acetic Acid Mixture.

Procedure A.

Epoxyisoindoline **6** (1.43 g, 5 mmole) was added to a mixture of 10 ml glacial acetic acid and 10 ml 66% hydrobromic acid. The reaction mixture protected from exposure to light was heated at 60-70 °C for 48 hours. The dark colored reaction mixture was poured into 100 ml of ice-cold water and neutralized to pH 6-7 with the 5% sodium hydroxide solution. The neutralized solution was extracted with ether (3x20 ml). The organic extracts were dried over the anhydrous magnesium sulfate and the solvent evaporated. The crude reaction product was subjected to silica gel column chromatography with petroleum ether/ether 5–10 % in the column protected from light.

N-(4-Methylphenyl)-6-bromo-5-hydroxy-4-methylisoindoline (**10**).

This compound (1.0 g, 64%, Rf=0.85) was obtained by evaporation of the more mobile fractions. Colorless crystals, mp. 174-175 °C; uv (methanol): λ_{max} 246, 275 nm (sh); ir (potassium bromide): ν 3460s (OH), 2920m, 2860m, 2820m, 1630s (C=C), 1530vs, 1470s, 1380vs, 1310vs, 1180m, 1070m, 850m, 800vs, 780s cm^{-1}; ^{1}H nmr (acetone-d_6): δ 7.74 (s, 1H, D_2O exchangeable) for C5-OH group, 7.37 (s, 1H) for isoindoline C7-H, 4.52 (s, 2H) for protons at C1; 4.53 (s, 2H) for protons at C3, 7.06 (d, 2H, J_{A2X2} = 8.5 Hz) and 6.62 (d, 2H, J_{A2X2} = 8.5 Hz) for p-phenylene protons at C3,5' and C2,6' respectively, 2.29 (s, 3H) for p-CH_3, 2.23 ppm (s, 3H) for isoindoline C4-CH_3; ^{13}C nmr (acetone-d_6): δ 53.0 (t) and 53.4 (t) for isoindoline 1-C and 3-C, 138.7 (s) for 3a-C, 120.1 (s) for 4-C, 149.2 (s) for 5-C, 108.9 (s) for 6-C, 122.6 (d) for 7-C and 130.7 (s) for 7a-C, 145.0 (s) for phenylene 1'-C, 111.4 (d) for 2'-C and 6'-C, 129.9 (d) for 3'-C and 5'-C, 125.4 (s) for phenylene 4'-C, 20.1 (q) for p-CH_3 and 12.9 ppm (q) for methyl group at isoindoline 4-C; ms (LDI, 337 nm): m/z (relative intensity) 319/317 (29/30, M^+ [^{81}Br/^{79}Br]), 318/316 (96/100, $[M-H]^+$), 238 (65), 237 (45), 184 (15), 120 (10), 118 (10), 91 (20) and 52 (60) ; hrms: $[M^+]$ calc'd for $C_{16}H_{16}{}^{79}BrNO$: 317.04153; found: 317.04071 [^{79}Br].

Anal. Calc'd. for $C_{16}H_{16}BrNO$ (M_r= 318.21): C 60.39, H 5.07, N 4.40%; found: C 60.28, H 5.01, N 4.28%.

N-(4-Methylphenyl)-7-bromo-4-methyl-5-nitro-3a,4,5,6,7,7a-hexahydro-5,7a-epoxyisoindoline (**8**).

This compound (200 mg, 11%, Rf=0.42) was obtained from slower moving fractions. Colorless crystals melting at 232-234 °C; ir (potassium bromide): ν 3020w, 2960m, 2930w, 2905w, 2880w, 2840m, 1615m, 1550s, 1515s, 1470m, 1455m, 1440m, 1360s, 1335m, 1270w, 1180m, 1110w, 1070m, 950m, 905w, 855m, 830m, 800s, 740w and 630w cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.78 (d, 1H, J = 13.5 Hz) and 3.73 (d, 1H, J = 13.5 Hz) for protons at C1, 3.94 (t, 1H, J = 8.7 Hz) and 3.28 (t, 1H, J = 8.7 Hz) for protons at C3, 2.27-2.21 (m, 1H) for C3a-H, 2.66-2.57 (m, 1H) for C4-H, 1.30 (d, 3H, J = 7.1 Hz) for methyl at C4, 3.40 (dd, 1H, J_1 = 14.0 Hz, J_2 = 7.5 Hz) and 2.71 (dd, 1H, J_1 = 14.0 Hz, J_2 = 3.0 Hz) for protons at C6, 4.35 (dd, 1H, J_1 = 7.5 Hz, J_2 = 3.0 Hz) for C7-H, 7.05 (d, 2H, J_{A2X2} = 8.2 Hz) and 6.48 (d, 2H, J_{A2X2} = 8.2 Hz) for p-phenylene protons at C3,5' and C2,6' respectively and 2.26 ppm (d, 3H, J = 7.1) for p-CH_3; ^{13}C nmr (deuteriochloroform): δ 52.6 (t) [19] and 55.2 (t) for 1-C and 3-C, 52.6 (d) [19] for 3a-C, 47.2 (d) and 46,8 (d) for 4-C and 7-C, 14.5 (q) for carbon of methyl group at 4-C, 112.4 (s) for 5-C, 41.2 (t) for 6-C, 94.8 (s) for 7a-C, 144.8 (s), 112.2 (d), 129.9 (d) and 126.4 (s) ppm for phenylene 1'-C, 2'-C, 3'-C and 4'-C respectively, and 20.1 ppm (q) for methyl of p-tolyl group; ms (LDI, 337 nm): m/z (relative intensity) 368/366 (15/15, M^+ [^{81}Br/^{79}Br]), 367/365 (49/50, $[M-H]^+$), 322 (10), 320 (10), 318 (15), 316 (15), 289 (15), 287 (15), 280 (10), 279 (50), 241 (25), 240 (100), 238 (30), 210 (10), 184 (20) 143 (10) and 141 (10); hrms: $[M^+]$ calc'd for $C_{16}H_{19}{}^{79}BrN_2O_3$: 366.05790; found: 366.05169 [^{79}Br].

Anal. Calc'd. for $C_{16}H_{19}N_2O_3$ (M_r=367.24): C 52.33, H 5.21, N 7.63%; found: C 52.35, H 5.19, N 7.61%.

Procedure B.

Similarly as in procedure A, but at lower temperature and with substantially higher quantity of hydrobromic acid/acetic acid mixture. Epoxyisoindoline **6** (1.43 g, 5 mmole) was added to 40 ml of acid mixture and was heated in the reaction vessel protected from light at 40-50 °C. After 48 hours of heating and usual elaboration hexahydroisoindoline **7** was isolated. The remaining material was starting compound **6** (more than 90 %) and traces of some resinous material.

N-(2-Bromo-4-methylphenyl)-4-methyl-5-nitro-3a,4,5,7a-tetrahydro-5,7a-epoxyisoindoline (**7**).

This compound was obtained as yellow crystals (91 mg, 5%) melting at 171-173 °C; ir (potassium bromide): ν 3080w, 2920m, 2840w, 1620m, 1560s, 1530s, 1480m, 1460w, 1410w, 1380m, 1360s, 1310w, 1270w, 1230w, 1170m, 1150m, 1120m, 1040w, 1000w, 950m, 900w, 860m, 840m, 800s, 710s and 690w cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.0 (d, 1H, J = 5.6 Hz) and 6.76 (d, 1H, J = 5.6 Hz) for C7-H and C6-H, 4.53 (d, 1H, J = 12.5 Hz) and 3.18 (d, 1H, J = 12.5 Hz) for protons at C1, 3.70 (t, 1H, J =

9.5 Hz) and 3.27 (t, 1H, J = 9.5 Hz) for protons at C3, 2.04 (dt, 1H, J_1 = 9.5 Hz, J_2 = 3.0 Hz) for C3a-H, 2.55 (dq, 1H, J_1 = 7.0 Hz, J_2= 3.0 Hz) for C4-H, 1,10 (d, 3H, J = 7.0) for methyl protons at isoindoline C4, 7.35 (dd, 1H, J_2= 1.3 Hz), 7.07 (dd, 1H, J_1 = 8.5 Hz, J_2 = 1.3 Hz) and 7.01 (d, 1H, J = 8.5 Hz) and for protons at aryl carbons C3', C5' and C6' respectively and 2.23 ppm (s, 3H) for p-CH_3; ^{13}C nmr (deuteriochloroform): δ 139.6 (d) and 131.3 (d) for isoindoline unsaturated 7-C and 6-C respectively, 115.0 (s), 95.1 (s), 55.8 (t), 53.0 (t), 53.7 (d) and 44.4 (d) for isoindoline saturated 5-C, 7a-C, 1-C, 3-C, 3a-C and 4-C respectively, 15.5 (q) for methyl carbon at isoindoline 4-C, 145.4 (s), 115.7 (s), 134.6 (d), 132.9 (s), 129.0 (d) and 119.7 (d) for p-phenylene carbons 1'-C, 2'-C, 3'-C, 4'-C, 5'-C and 6'-C respectively, 19.4 ppm (q) for carbon of p-methyl group; ms (EI, 20 eV): m/z (relative intensity) 367/365 (20/20, $[M+H]^+$), 366/364 (97/100, M^+ [^{81}Br/^{79}Br]), 333 (10), 332 (15), 331 (10), 330 (15), 312 (24), 310 (25), 287 (25), 286 (40), 285 (25), 266 (15), 257 (40), 239 (10) and 184 (10); hrms: [M^+] calc'd for $C_{16}H_{17}{}^{79}BrN_2O_3$: 364.04225 , found: 364.03644 [^{79}Br].

Procedure C.

In a repeated experiment with the same quantity of **6** as in procedure B, during heating at 40-50 °C for 5 days, two additional portions of the same acid mixture (2x20 ml) were added. Column chromatography after a careful neutralization of reaction mixture yielded 318 mg (20%) of the compound **10** which was identical with the sample from procedure A and pure dibromo derivative **11**.

N-(2-Bromo-4-methylphenyl)-6-bromo-5-hydroxy-4-methylisoindoline (**11**).

This compound was obtained as colorless micro crystals (1.03 g, 52%) melting at 120-122 °C (Rf=0.9); uv (methanol): λ_{max} 220, 245 (sh); ir: ν 3420s (OH), 2925s, 2860m, 1620s (C=C), 1510vs, 1465vs, 1370vs, 1320s, 1260m, 1220m, 1070s, 860s, 790vs, 780s cm^{-1}; ^{1}H nmr (acetone-d_6): δ 7.70 (s, 1H, D_2O exchangeable) for C5-OH, 7.33 (s, 1H) for isoindoline C7-H, 4.61 (s, 2H) for protons at C1, 4.64 (s, 2H) for protons at C3, 7.42 (d, 1H, J = 1.4 Hz), 7.13 (dd, 1H, J_1 = 1.4 Hz, J_2 = 8.5 Hz) and 7.21 (d, 1H, J = 8.5 Hz) for protons C3'-H, C5'-H and C6'-H, 2.27 (s, 3H) for protons of p-CH_3, and 2.24 ppm (s, 3H) for protons of isoindoline C4-CH_3; ^{13}C nmr (acetone-d_6): δ 55.7 (t) for isoindoline 1-C, 56.2 (t) for 3-C, 139.3 (s) for 3a-C, 119.9 (s) for 4-C, 149.1 (s) for 5-C, 108.6 (s) for 6-C, 122.4 (d) for 7-C, 131.6 (s) for 7a-C, 20.1 (q) for methyl group at isoindoline 4-C, 145.1 (s) for p-phenylene carbon 1'-C, 115.6 (s) for 2'-C, 135.0 (d) for 3'-C, 132.7 (s) for 4'-C, 128.7 (d) for 5'-C and 119.7 (d) for 6'-C, and 13.0 ppm (q) for p-methyl carbon; ms (EI, 85 eV): m/z (relative intensity) 399/397/395 (24/50/25, M^+ [^{81}Br/^{79}Br]), 398/396/394 (49/100/50, $[M-1]^+$), 319 (25), 318 (30), 317 (40), 316 (30), 315 (30), 237 (10), 111 (20), 109 (20), 97 (25), 95 (30) and 91 (30); hrms: [M^+] calc'd for $C_{16}H_{15}{}^{79}Br_2NO$: 394.95204, found: 394.94973 [^{79}Br].

Anal. Calc'd. for $C_{16}H_{15}Br_2NO$ (M_r= 397.10): C 48.39, H 3.81, N 3.53%; found: C 48.53, H 3.95, N 3.64%.

Single Crystal X-ray Structural Determination of **11**.

Colorless monoclinic crystals in a form of thin needles were obtained by repeated recrystallization from acetone/water 5:2. Suitable crystals were formed on very slow crystallization during 5 days at –3 °C. Data collection was carried out on the KappaCCD Nonius diffractometer. Program Denzo-SMN [20] was used for data reduction. No absorption correction has been applied, only scaling. Structure has been solved using the SHELXS97 program [21]. All non-hydrogen atoms were refined anisotropically based on F^2 by full-matrix least-squares method. All hydrogen atoms were included in calculated positions as riding atoms with the SHELXL97 [18] default parameters.

N-(2-Bromo-4-methylphenyl)-7-bromo-4-methyl-5-nitro-5,7a-epoxy-3a,4,5,6,7,7a-hexahydroisoindoline (**9**).

During chromatographic separation of the crude reaction products beside **10** and **11** as described above a small quantity of compound **9** was separated. Light yellow crystals (112 mg, 5%, Rf=0.62) melting at 86-88 °C; ir (potassium bromide): ν 3010w, 2960w, 2920s, 2840m, 1605m, 1550s, 1490s, 1460m, 1360m 1320m, 1260m, 1160m, 1050m, 950m, 830m, 830m, 810s, 750m, 600s cm^{-1}; ^{1}H nmr (acetone-d_6): δ 4.21 (d, 1H, J = 12.0 Hz) and 3.37 (d, 1H, J = 12.0 Hz) for protons at C1, 3.75 (t, 1H, J = 9.0 Hz) and 3.44 (t, 1H, J = 9.0 Hz) for protons at C3, 2.45 (dt, 1H, J_1 = 9.0 Hz, J_2 = 4.7 Hz) for C3a-H, 2.67-2.61 (m, 1H) for C4-H, 1.32 (d, 3H, J = 7.0 Hz) for methyl at C4, 3.62 (dd, 1H, J_1 = 14.5 Hz, J_2 = 7.5 Hz) and 2.67 (dd, 1H, J_1 = 14.5 Hz, J_2 = 3.0 Hz) for protons at C6, 4.85 (dd, 1H, J_1 = 7.5 Hz, J_2 = 3.0 Hz) for C7-H, 7.40 (d, 1H, J = 2.0 Hz), 7.14 (dd, 1H, J_1 = 8.2 Hz, J_2 = 2.0 Hz) and 7.08 (d, 1H, J = 8.2 Hz) for protons C3', C5' and C6' at aryl group respectively and 2.27 ppm (s, 3H) for p-CH_3; ^{13}C nmr (acetone-d_6): δ 55.3 (t) and 58.0 (t) for 1-C and 3-C, 52.5 (d) for 3a-C, 46.6 (d) and 49.0 (d) for 4-C and 7-C, 13.5 (q) for carbon of methyl group at 4-C, 113.0 (s) for 5-C, 41.8 (t) for 6-C, 95.4 (s) for 7a-C, 145.0 (s), 115.8 (s), 134.6 (d), 133.6 (s), 129.1 (d) and 102.0 (s) for aromatic 1'-C, 2'-C, 3'-C, 4'-C, 5'-C and 6'-C respectively and 19.5 ppm (q) for carbon of p-methyl group; ms (EI, 70 eV): m/z (relative intensity) 448/446/444 (48/100/50, M^+ [^{81}Br/^{79}Br]), 398 (6), 396 (10), 394 (6), 367 (30), 365 (30), 320 (15) and 318 (15); hrms: [M^+] calc'd for $C_{16}H_{18}{}^{79}Br_2N_2O_3$: 443.96841 , found: 443.95691 [^{79}Br].

Anal. Calc'd. for $C_{16}H_{18}N_2O_3$ (M_r=446.13): C 43.07, H 4.07, N 6.28%; found: C 43.29, H 4.23, N 6.32%.

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REFERENCES AND NOTES

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