JOC Article

Wagner−Meerwein Skeletal Rearrangement of 3-Spiroannulated 6,8a-Epoxy- and 6,8a;7,8-Diepoxyisoquinolines (3-Aza-11-oxatricyclo[6.2.1.0^{1,6}]undec-9-enes). Isolation and Identification of 5-Aza-2-oxatricyclo[6.2.1.0^{3,9}]undec-3-enes

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The reactions of 3-acetyl-3-aza-11-oxatricyclo[6.2.1.0^{1,6}]undec-9-ene and its 9,10-epoxy derivative with bromine and $Ac_2O/BF_3{\cdot}OEt_2$ under different conditions were studied. Unusual products of Wagner−Meerwein rearrangement bearing the olefin fragment (5-aza-2-oxatricyclo[6.2.1.0^{3,9}]-undecen-3-enes) were isolated and characterized by X-ray analysis.

Introduction

The skeletal rearrangement of isoborneol to camphene[1] was discovered by Wagner in 1899. It was thoroughly studied by Meerwein later.[2] This rearrangement is quite common in organic chemistry and can occur in more than terpene chemistry. Retropinacolic, Bertram−Walbaum,[3] Demjanov−Tiffeneau,[4] and Nametkin rearrangements[5] are analogues of this reaction. The transformation of α-campholic acid into isolauric acid in the presence of diluted sulfuric acid is an example of Wagner−Meerwein rearrangement in a series of monocyclic compounds.[6] Wagner−Meerwein rearrangement and its analogues proceed through a cationic center as an intermediate and are accompanied by the migration of alkyl substituents to this center. In bicyclic terpenes, the Wagner−Meerwein rearrangement is frequently observed and accompanied not only by radical migration, but by *exo*-migrations of hydrogen atoms as well.[7] Usually, as a stereochemical result of such rearrangement, an inversion of the final migration center is observed and this phenomenon is widely used in stereoselective synthesis of natural terpene derivatives.

Wagner−Meerwein (pinacolic) rearrangement of 7-oxabicyclo[2.2.1]hept-2-yl derivatives is used for the synthesis of carbohydrates.[8] The mechanism of the reaction is described in a great number of publications.[9]

Recently, 7-oxabicyclo[2.2.1]heptanes condensed with cyclohexane, piperidine, and pyrrolidine cycles have become available. Tricyclic compounds of this type are easily prepared by Diels−Alder reaction from the corresponding alkenyl- and (*N*-alkenylamino)furans.[10] Compounds interesting from theoretical and practical points of view can be synthesized from these tricyclic compounds by using Wagner−Meerwein rearrangement. However, only a few examples of this rearrangement for epoxyoctahydronaphthalenes and epoxyhexahydroisoindolines have been studied. So far, this type of reaction of 6,8a-epoxyhexahydroisoquinolines is unknown.

Rearrangement of 4a,7-epoxyoctahydronaphthalene-1-ones (**1**) with iodine under Woodward reaction conditions

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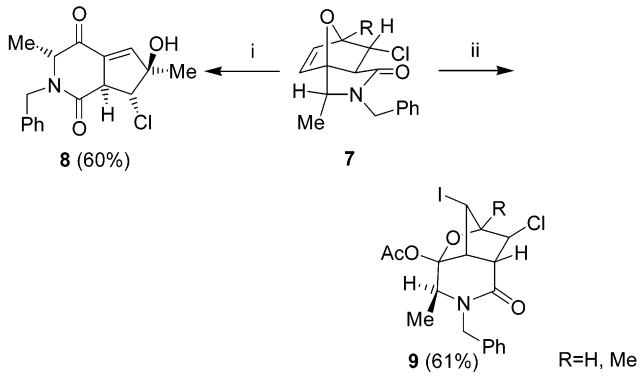
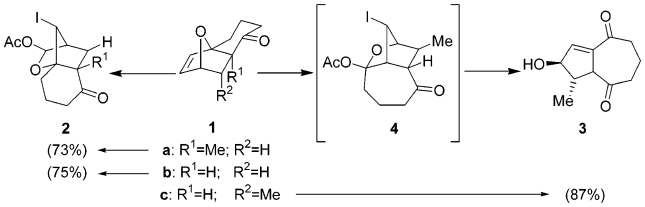
SCHEME 1[a]



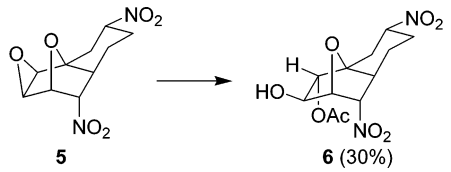
[a] Reagents and conditions: (i) NBS, aq DMSO, 25 °C, 3 h; (ii) AgOAc, aq Ac_2O, 25 °C, 20 h.

(I_2, AgOAc, aq AcOH, and then aq Na_2CO_3) was studied for the first time in 1989 by Keay.[11]



Thus, treatment of the tricycles **1a**,**b** with iodine gave tricyclic products **2** (common for Wagner−Meerwein rearrangement). Under the same conditions, compound **1c** was transformed to the condensed derivative **3** in good yield. The authors suggested that this derivative might be a product of intermediate **4**—the second product of the rearrangement. However, the authors did not provide any proof of its formation.

Later, the treatment of diepoxyoctahydronaphthalene **5** with Ac_2O in the presence of catalytic amount of $BF_3 \cdot OEt_2$ (25 °C, 24 h) gave only monoepoxydecaline **6** in poor yield (30%).[12] The isolated tricycle **6** was a product of the *exo*-oxirane ring cleavage. Under these conditions, no Wagner−Meerwein rearrangement product was isolated.



Chemical behavior of epoxyhexahydroisoindolinones **7** was studied under different conditions (Scheme 1).[13]

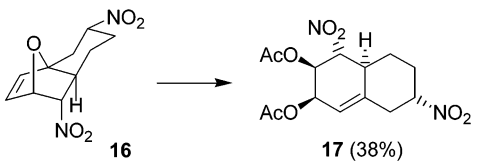
The authors[13] demonstrated that the interaction of bridged polycyclic compounds **7** with NBS in DMSO led to the opening of both the nitrogen containing ring and cyclohexane moiety with recyclization to form cyclopenta-[c]piperidine system **8**, while under Woodward reaction conditions the same compound **7** yielded tricyclic derivatives **9** as a result of Wagner−Meerwein rearrangement. However, in the paper there were no explanations of high stereoselectivity of the reaction or any intermediates and byproducts data.

Results and Discussion

Decahydroisoquinoline system is a structural fragment of more than 500 alkaloids;[14] that is why synthesis and chemistry of this heterocyclic system are very important and promising. As a part of our research program for the study of *N*-heterocyclic compounds, an efficient one-stage synthesis of 3-spiroannulated hydrogenated 6,8a-epoxyisoquinolines (3-aza-11-oxatricyclo[6.2.1.0^{1,6}]undecenes) **10** using the available 1-allyl-1-*N*-(α-furfurylamino)-cycloalkanes has been developed recently.[15] As these 6,8-epoxyisoquinoline derivatives might be promising synthons to obtain polyhydroxyl-substituted hydrogenated isoquinolines, we prepared new epoxyisoquinolines **10a**,**b** spiroannulated with cyclohexane and cycloheptane rings and planned to study their reactivity in order to find the ways of the epoxide ring disclosure (Scheme 2).

First, in the presence of $BF_3 \cdot OEt_2$ in acetic anhydride compound **10a** was transformed into spiro[isoquinolinocyclohexane] **11** (yield 56%). This reaction was a result of opening of the oxa-bridge with subsequent migration of the double bond. Its structure was established by ^1H and ^{13}C NMR spectroscopic data. The fact of double bond migration to Δ^8-position was proved by the presence of quaternary carbon at δ 141.7 ppm. Ralatively high (for diacetoxysubstituted fragments) coupling constant $^3J_{6-H,7-H}$ = 8.0 Hz indicated pseudoaxial positions of 6-H and 7-H. It means that the acetoxy groups had trans configuration. This conclusion was confirmed by ^1H NMR NOE values indicating the increase of H_i signal intensivity when H_j signal was saturated ($\eta_{Hi}\{H_j\}$, %). The values of $\eta_{6-H}\{4a\text{-}H\}$=7.5%, $\eta_{6-H}\{5_{eq}\text{-}H\}$ = 10% and $\eta_{4a-H}\{5_{eq}\text{-}H\}$ = 4.5%, on one hand, and $\eta_{7-H}\{5_{ax}\text{-}H\}$ = 5.5%, on the other hand, proved that 4a-H, 5_{eq}-H, and 6-H atoms were situated on the one side of the cyclohexane plane and 7-H and 5_{ax}-H atoms on the other side of the plane.

It is interesting to note that in another work[12] it was shown that the product **17** with *cis*-orientation of acetoxy groups in the cyclohexane ring was obtained from 3,7-dinitro-11-oxatricyloundec-9-ene (**16**) under similar conditions.



Then, the epoxidation of the double bond in **10a**,**b** was accomplished by peroxyformic acid generated in situ. The yields of diepoxides **12a**,**b** were 85−92%, which was 7−10% higher than in the case of *m*-chloroperoxybenzoic acid which is the most frequently used chemical for

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(12) Sader-Bakaouni, L.; Charton, O.; Kunesch, N.; Tillequin, F. *Tetrahedron* **1998**, *54*, 1773.
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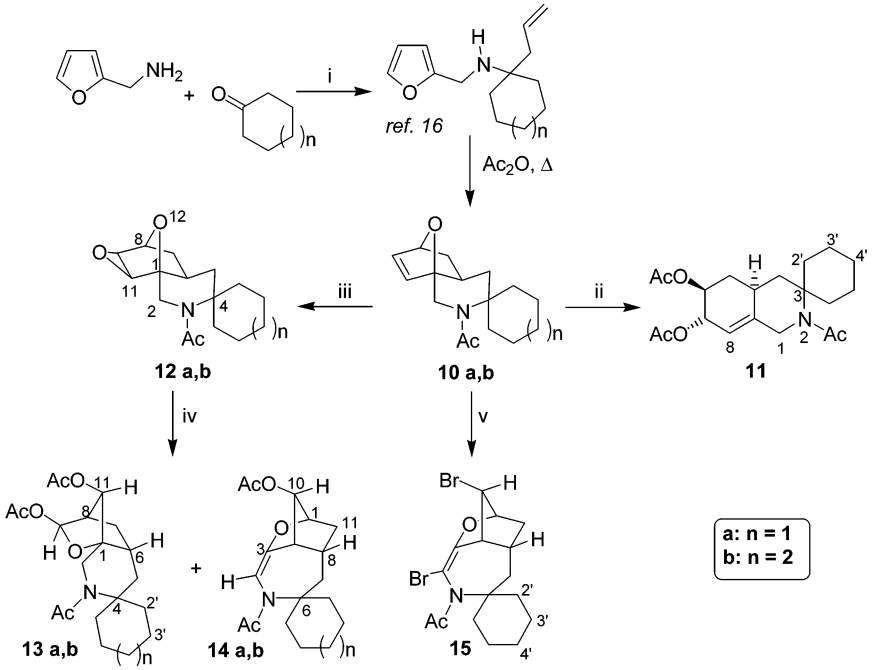
SCHEME 2[a]



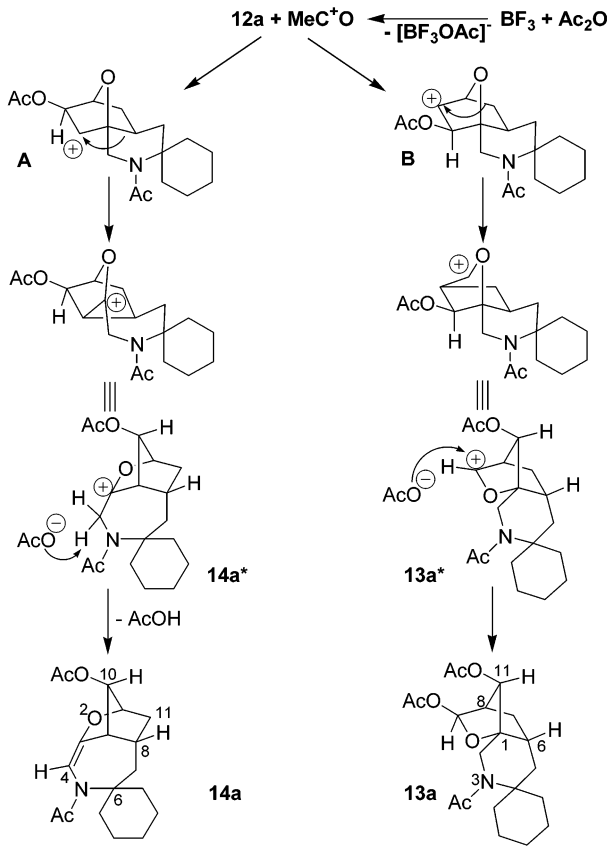
[a] Reagents and conditions: (i) PhH, Δ, then allylMgBr/Et_2O; (ii) BF_3·OEt_2/Ac_2O, 25 °C, 1 h; (iii) H_2O_2 (50%)/HCOOH, Δ, 3 h; (iv) BF_3·OEt_2/Ac_2O, 0 °C, 1 h; (v) NBS/ *m*-CPBA, $CHCl_3$, Δ, 2.5 h

epoxidation of norbornene and 7-oxabicylo[2.2.1]heptene derivatives.

As expected,[12] oxirane ring of tetracycles **12a**,**b** was *exo*-annulated to oxabicycloheptane fragment. *Endo*-configuration of 6-H, 9-H, 11-H, and 7A$_{(endo)}$-H of the compound **12a** was determined by NOE values in ^{1}H NMR experiment (η_{11-H}{6-H} = 2.7% → η_{9-H}{7A$_{(endo)}$-H}=3.8%). By comparison of vicinal constants $^3J_{7\ A(endo)-H,\ 8-H}$ < 1 Hz, $^3J_{7B(exo)-H,\ 8-H}$ =4.9 Hz → $^3J_{8-H,\ 9-H}$ < 1 Hz with the literature data for analogous bridged systems such configuration was also confirmed.[17] According to these data spin coupling constant of proton in the head of the bridge is very small (<1 Hz) for α-*endo*-H, but it is higher than 3 Hz for α-*exo*-H, so the observed spin coupling constants unambiguously prove *endo*-orientation of 9-H and 7A$_{(endo)}$-H. The vicinal couplings $^3J_{6-H,7A(endo)-H}$ = 8.0 Hz and $^3J_{6-H,7B(exo)-H}$=3.7 Hz confirm the same (*endo*) orientation of 6-H as well.

The exposure of diepoxides **12a,b** with BF_3·OEt_2 in the presence of acetic anhydride led to the opening of oxirane ring in accordance with the Wagner-Meerwein (pinacolic) skeleton rearrangement (Scheme 2). As a result two products **13a,b** and **14a,b** (in nearly equal amounts) were formed via alternative cations **A** and **B** (Scheme 3). It should be noticed that compounds similar to **13a** and **13b** are frequently formed by skeletal rearrangements of more simple bicyclic systems (for example **9**),[9a,18] while the unsaturated azepines **14a** and **14b** were described by us for the first time.

SCHEME 3

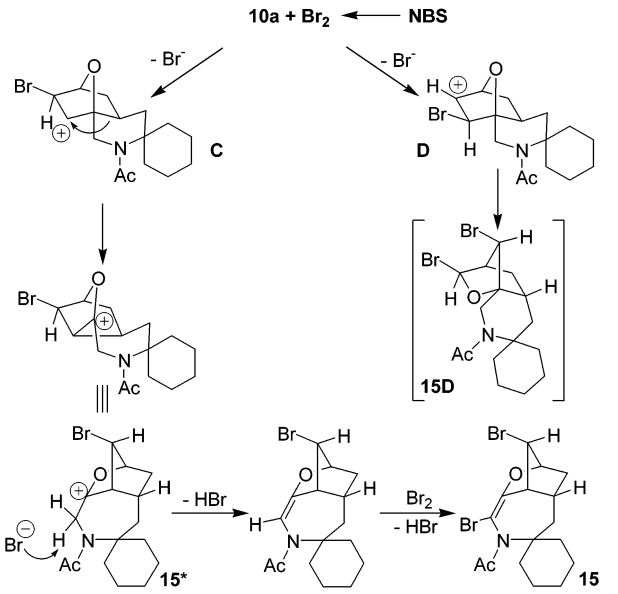


The formation mechanism of **13** and **14** looks like a typical Wagner−Meerwein rearrangement and it is exemplified by the tetracycle **12a** conversion on the Scheme 3.

(16) (a) Varlamov, A. V.; Kouznetsov, V. V.; Zubkov, F. I.; Chernyshev, A. I.; Alexandrov, G. G.; Palma, A. R.; Vargas, L.; Salas, S. *Synthesis* **2001**, *6*, 849−854. (b) Varlamov, A. V.; Kouznetsov, V. V.; Zubkov, F. I.; Chernyshev, A. I.; Shurupova, O. V.; Vargas Méndez L. Y.; Palma, A. R.; Castro, J. R.; Rosas-Romero, A. J. *Synthesis* **2002**, *6*, 771−783.

(17) Nelson, W. L.; Allen, D. R. *J. Heterocycl. Chem*. **1972**, *9*, 561−568.

SCHEME 4



The attack of acyl cation on oxygen atom of the *exo*-oxirane ring leads to its opening to form cations **A** or **B**. The following migration of the neighboring σ-bonds in these cations forms intermediate ions **14a*** and **13a***. Cation **13a*** is stabilized by attaching the acetoxy anion from the less sterically hindered side, while ion **14a*** eliminates one of hydrogen atoms from the neighboring to cationic center methylene (4-CH_2) group and forms the compound **14a**. The cationic center in **14a*** appears to be sterically highly shielded by tricyclic skeleton and cannot be stabilized by attaching bulky acetoxy group.

Probably, reaction paths undergoing through intermediates **A** and **B** have the same rate as the compounds **13** and **14** are formed in equal amounts.

Similar skeletal rearrangement takes place in epoxyisoquinoline **10a** in the presence of NBS and catalytic amounts of *m*-CPBA. Tetrahydroazepine **15** which is a structural analogue of **14** was isolated from the reaction mixture by using 2-fold excess of NBS. Dibromo-substituted compound **15** is formed by skeletal rearrangement of intermediate cation **C** (Scheme 4).

It is worth noting here that in another case reported by Jung,[13a] a similar rearranged product was not isolated from the reaction of NBS under the same conditions with 3-aza-10-oxatricyclo[5.2.1.0^{1,5}]dec-8-ene **7.**

We were not able to isolate an expected product (**15D**) of alternative rearrangement of cation **D** (Scheme 4), possibly due to the high mobility of bromine atoms. Wagner-Meerwein rearrangement of **10a** in the absence of *m*-CPBA proceeded slower. The bromination of the tricycle **10a** under different conditions (Br_2/CCl_4, Br_2/AcOH, NBS/DMSO) gave rise to the formation of complex reaction mixtures, and neither products of the skeletal rearrangement or products of addition to the double bond could be isolated. Halogen substituted compound **15** was a rather stable compound, but it quickly became dark on light exposure without changing its chemical and spectral properties.

The structure of compounds **13a** and **13b** was proved by ^{1}H and ^{13}C NMR spectral data. It should be underlined that in ^{13}C NMR spectra of both compounds there was a signal at δ ~98.8 ppm (**13a**: δ 98.8, $^1J_{CH}$=180.8 Hz; **13b**: δ 98.5 ppm), assigned to tertiary sp^3-hybridized carbon atom C_9, bonded with two electronegative atoms (O_{10} and OAc). In ^{1}H NMR spectra a singlet signal of 9-H ($^3J_{8-H,9-H}$ < 1 Hz) proved its *endo*-orientation. This conclusion was confirmed by NOE high value η_{9-H}{7A-H} = 12% for the compound **13a**, which was possible only for *endo*-orientation of both hydrogen atoms (9-H and 7A-H). Vicinal coupling constants of 7A-H and 7B-H ($J_{7A-H,8-H} \leq 1$ Hz, $J_{7B-H,8-H} = 4.8$ Hz, $J_{7A-H,6-H} = 5.0$ Hz, $J_{7B-H,6-H} = 10.7$ Hz) were in accordance with assignment of these protons to $H_{(endo)}$ and $H_{(exo)}$, respectively.[17] The constants also pointed out the 6-H *exo*-orientation in compound **13a** that was in contrast to the 6-H *endo*-orientation in compounds **10** and **12**. On the basis of these facts it is possible to make a conclusion that in the process of Wagner−Meerwein rearrangement of the epoxide **12** to the tricycle **13** the inversion of C_6 configuration took place.

The 6-H *exo*-orientation in **13a** was also confirmed by NOE high value η_{6-H}{11-H} = 13% showing spatial proximity of 6-H and 11-H. This proximity is possible only with *cis*-orientation of 6-H and 11-H in cyclopentane ring, on one hand, and C_{11}−O- orientation to C_9−O_{10}, on the other hand.

The other vicinal couplings and NOE values for the compound **13a**, in particular $^3J_{6-H,5A-H}$ = 4.2 (J_{gauche}), $J_{6-H,5B-H}$ = 12.5 Hz (J_{trans}), η_{8-H}{9-H} = 6%, η_{8-H}{11-H} = 6%, η_{11-H}{7-H_B} = 5%, were in full agreement with its structure. An analogous structure might be deduced for the compound **13b** (homologue of **13a**) because its ^{1}H and ^{13}C spectral parameters are very similar to those of the compound **13a**.

^{1}H and ^{13}C NMR data for the compounds **14a, 14b** and **15** manifest the structure similarity for all these compounds. But at the same time they differ from the spectral data of the initial compounds **10** and **12**. In particular, there is not any piperidine ring and there is C=C double bond in the vicinal position to NAc grouping. However the absence of literature analogy of the structure of the compound **14** did not allow to make a choice between bridged azepine structure (**14**) and some other alternative structures, in particular, the bridged systems with *N*-acetylpyrrolidine cycle, based only on NMR data.

Monocrystals were generated by crystallization of **14a** and **15** from the mixture of hexane with ethyl acetate, and their molecular structures were unambiguously elucidated by X-ray data (Figure 1).[19]

In both compounds tetrahydroazepine fragment has "flat tub" conformation, and deviation of N(1), C(1), and C(4) atoms from the plane of other four carbons in tricyclic compound **14** is 1.18, 1.06, and 0.75 Å, and in **15** 1.18, 1.05, and 0.74 Å (Figure 1). Nitrogen atom is

(18) (a) Bernson, J. A.; Swidler, R. *J. Am. Chem. Soc.* **1953**, *75*, 1721−1726. (b) Imagawa, T.; Nakagawa, T.; Matsuura, K.; Akiyama, T.; Kawanisi, M. *Chem. Lett.* **1981**, 903. (c) Vogel, P.; Fattori, D.; Gasparini, F.; Le Drian, C. *Synlett* **1990**, 173−185.

(19) The authors have deposited the X-ray data of compounds **14** and **15** with the Cambridge Crystallographic Data Centre (CCDC) as supplementary publication nos. CCDC 219626 (**15**) and 219625 (**14a**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

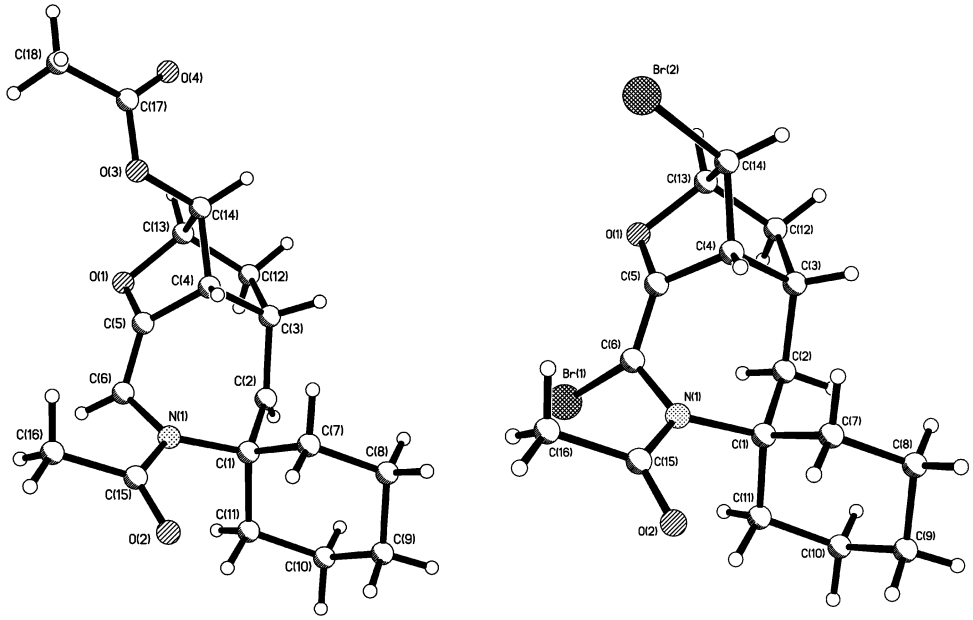


FIGURE 1. X-ray crystal structures of **14a** and **15**.

equatorial in cyclohexane rings (for example, in **15** deviation of N(1) from the C6C8C10C11 plane is 0.46 Å as for C(2) is 2.16 Å). It should be noticed that geometry of strained unsaturated fragment in tricyclic compounds **14a** and **15** is unusual. Inclusion of O(1), C(4), and N(1) atoms into the strained tricylic system and steric interaction between bulky bromine atom and acetyl group C(15)O(2)C(16) cause certain violation of the trigonal configuration (pyramidal flatness) of ethylene bond atoms C(5)═C(6). For example, the sum of valence angles of C(5) in **14** and **15** is 357.3° and 357.6° whereas at C(6) in bromine substituted compound **15** it is 357.6° (crystallographic numbering used everywhere). Such distortion leads to serious violation of the ethylene fragment plane in these structures—deviation of C(5) and C(6) from the N1Br1C4O1 plane is 0.22 Å, and two side angle between Br1C6C5O1 and N1C6C5C4 planes is 160.8°. So the unsaturated fragment of **15** Br1NC6C5O1C4 is bent along C(6)═C(5) bond under ∼160° angle, that is serious deviation from usual plane geometry of olefin fragments. The presence of the less bulky hydrogen atom in **14a** (in comparison with bromine atom in **15**) leads to less violation of flat trigonal configuration of C(6) in **14a**. As a result, the unsaturated fragment of **14a** is less distorted. It is interesting that the noted violations of flatness of olefin fragments do not have any effect on C(6)═C(5) double bond length, which is 1.32 Å in **15**, and 1.33 Å in **14a**.

In conclusion, this work demonstrates a versatile new approach to spiroannulated 6,8a-epoxyisoquinolines (3-aza-11-oxatricyclo[6.2.1.0^{1,6}]undecenes) using accessible 1-allyl-1-*N*-(α-furfurylamino)cycloalkanes for the synthesis of several polyhydroisoquinoline alkaloids. Wagner−Meerwein rearrangement of 6,8a-epoxyisoquinolin-7-enes and its 7,8-epoxidation products under the action of bromine and BF_3·OEt_2/Ac_2O was studied. As a result, a new heterocyclic system (5-aza-2-oxatricyclo[6.2.1.0^{3,9}]-undecene-3-ene)—previously unknown product of Wagner−Meerwein rearrangement—was isolated and characterized by X-ray analysis.

Experimental Section

Melting points were uncorrected. IR spectra were obtained in KBr pellets for solids or in thin film for oils. NMR spectra (^{1}H 400 MHz, ^{13}C 100.6 MHz) were recorded for solutions in deuteriochloroform (all compounds except **13a**) at 23 °C; deuteriochloroform (^{13}C NMR, δ 76.9 ppm) and traces of chloroform (^{1}H NMR, δ 7.24 ppm) were used as the internal standard. Compound **13a** was studied in mixture of deuteriochloroform and deuteriobenzene (v/v ∼ 1/1); for the spectra deuteriobezene (^{13}C NMR, δ 128.0 ppm) and traces of pentadeuteriobenzene C_6D_5H (^{1}H NMR, δ 7.15 ppm) were used as the internal standard. Coupling constants are reported in Hz. The purity of the obtained substances and the composition of the reaction mixtures were controlled by TLC silufol UV_{254} plates. The separation of the final products was carried out by column chromatography on Al_2O_3 (activated, neutral, 50−200 μm) or by fractional crystallization.

Initial 4-annulated 11-oxa-3-azatricyclo[6.2.1.0^{1,6}]undec-9-enes **10a**,**b** were synthesized by the following method.[15]

10a. White crystals. Yield: 68%. Mp: 134−135 °C. MS (EI, 70 eV) *m*/*z* (rel intensity): 261 (M^+, 63), 220 (19), 218 (13), 204 (34), 176 (12), 140 (40), 122 (14), 121 (29), 81 (100), 43 (25), 40 (26). IR (KBr, ν/cm^{-1}): 1630 (C═O and C═C). ^{1}H NMR: 6.30 (dd, ^3J = 5.8, J = 1.7, H-9); 6.12 (d, ^3J = 5.8, H-10); 4.86 (dd, ^3J = 4.5, J = 1.7, H-8); 3.92 (d, ^2J = 15.4, H-2B); 3.75 (d, ^2J = 15.4, H-2A); 2.11 (s, $NCOCH_3$); 1.86 (dd, ^2J = 13.5, ^3J = 5.1, H-5B); 1.72 (m, H-6); 1.46 (dd, ^2J = 13.5, ^3J = 12.5, H-5A); 1.47 (dd, ^2J = 11.3, ^3J = 7.6, H-7-*endo*); 1.38 (m, ^2J = 11.3, ^3J = 4.5,3.4, H-7-*exo*), 2.64 and 1.25 (2H, m, H-2′), 2.84 and 1.40 (2H, m, H-6′), 1.50−1.35 (6H, m, H-3′, H-4′, H-5′). ^{13}C NMR: 172.1 (NCO); 137.0 (C_9, J = 174.5); 135.4 (C_{10}, J = 173.5); 85.9 (C_1); 78.2 (C_8, J = 163.5); 60.8 (C_4); 45.3 (C_2, J = 137.5); 37.5 (C_5, J = 128.8); 35.1 ($C_{6'}$); 32.4 (C_7, J = 135.0); 32.0 (C_6, J = 133.0); 31.0 ($C_{2'}$); 25.7 ($NCOCH_3$, J = 128.2); 22.1, 22.3, 25.5 ($C_{3'}$, $C_{4'}$, $C_{5'}$). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.56; H, 8.81; N, 5.36. Found: C, 73.36; H, 8.79; N, 5.24.

10b. White crystals. Yield: 66%. Mp: 135−136 °C. MS (EI, 70 eV) *m*/*z* (rel intensity): 275 (M^+, 45), 234 (12), 204 (24), 176 (11), 154 (41), 135 (18), 122 (11), 81 (100), 53 (10), 43 (18), 41 (11). IR (KBr, ν/cm^{-1}): 1623 (C═O and C═C). ^{1}H NMR (200 MHz, $CDCl_3$): 6.32 (s, 2H), 4.90 (d, 1H, J = 4.3 Hz), 4.04 (d, 1H, J = 15.0 Hz), 3.47 (d, 1H, J = 15.0 Hz), 2.14 (s, 3H, Me), 1.96 (dd, 1H, J = 11.3, J = 3.1 Hz), 1.41 (dt, 1H, J = 11.3, J

= 4.3 Hz), 1.2−2.0 (m, 15H) Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.18; H, 9.10; N, 5.10. Found: C, 74.27; H, 9.15; N, 5.26.

2-Acetyl-6,7-diacetoxy-1,2,3,4,4a,5,6,7-octahydrospiro-[isoquinoline-3,1′-cyclohexane] (11). BF_3·OEt_2 2.4 mL (19.0 mmol) was added to solution of 2.00 g (7.66 mmol) of compound **10a** in 30 mL of acetic anhydride. The dark brown reaction mixture was stirred at 25 °C during 1 h. Then it was diluted with water (100 mL), neutralized with Na_2CO_3, and extracted with ether (3 × 50 mL). The organic phase was dried by $MgSO_4$. After solvent distillation, the substance was recrystallized from mixture of ethyl acetate−hexane to give 1.57 g (4.30 mmol) of compound **11**. White crystals. Mp: 129−132.5 °C. R_f: 0.21 (ethyl acetate−hexane, 2:1). Yield: 56%. IR (ν, cm^{-1}): 1638 (N−C═O), 1725 (O−C═O). MS (EI, 70 eV), *m*/*z* (rel intensity): 363 (M$^+$, 2), 306 (10), 304 (10), 303 (12), 202 (8), 184 (5), 106 (11), 91 (12), 79 (8), 67 (6), 55 (6), 43 (100), 41 (7). ^{1}H NMR: 5.42 (dt, ^3J = 8.0, 2.6, ^4J = 2.6, H-7); 5.31 (m, ^3J = 2.6, ^4J = 2.0, 1.2, H-8); 5.02 (m, ^3J = 12.3, 8.0, 4.2, H-6); 3.92 (dd, ^2J = 16.8, ^4J = 1.2, H-1A); 3.84 (m, ^2J = 16.8, ^4J = 2.0, 2.0, ^5J = 2.0, H-1B); 2.53 (m, H-4a); 2.04 (s, $NCOCH_3$); 2.04 (m, ^2J = 12.3, ^3J = 4.2, 4.2, H-5B); 2.02 (s, $OCOCH_3$); 2.01 (s, $OCOCH_3$); 1.91 (dd, ^2J = 13.6, ^3J = 4.0, H-4B); 1.42 (m, ^2J = 12.3, ^3J = 12.3, 11.4, H-5A); 1.24 (t, ^2J = 13.6, ^3J = 13.0, H-4A); 1.40 and 2.69 (2H, m, H-2′); 1.30 and 2.86 (2H, m, H-6′); 1.60−1.30 (6H, m, H-3′, H-4′, H-5′). ^{13}C NMR: 171.1 (NCO); 170.6 (OCO); 170.4 (OCO); 141.7 (C_{8a}); 117.1 (C_8, J = 160.8); 72.8 (C_7, J = 150.3); 72.1 (C_6, J = 150.4); 60.6 (C_3); 47.1 (C_1, J = 137.7); 38.3 (C_4, J = 128.0); 34.1[a] (C_5); 34.0[a] ($C_{2'}$); 30.7 (C_{4a}); 29.7 ($C_{6'}$); 22.4, 22.6, 25.1 ($C_{3'}$, $C_{4'}$, $C_{5'}$); 25.6 ($NCOCH_3$, J = 127.9); 20.99 ($OCOCH_3$, J = 129.8), 20.96 ($OCOCH_3$, J = 129.7). Anal. Calcd for $C_{20}H_{29}NO_5$: C, 66.11; H, 7.98; N, 3.85. Found: C, 66.05; H, 8.00; N, 3.86.

3-Acetylspiro[3-aza-10,12-dioxotetracyclo[6.3.1.0^{1,6}.0^{9,11}]-dodecane-4,1′-cyclohexane] (12a). A mixture of 2.0 mL (51.7 mmol) of formic acid and 1.0 mL (68.9 mmol) of 50% hydrogen peroxide was added to solution of 3.00 g (11.49 mmol) of adduct **10a** in 25 mL of chloroform. The reaction mixture was boiled for 3 h (monitoring by TLC). Then it was diluted with water (50 mL), neutralized with $NaHCO_3$, and extracted with chloroform (3 × 50 mL). The organic phase was dried over $MgSO_4$. After solvent distillation, the substance was recrystallized from mixture of hexane−chloroform to give 2.70 g (9.74 mmol) of compound **12a**. White crystals. Mp: 173−174 °C. R_f: 0.50 (ethyl acetate). Yield: 85%. IR (ν, cm^{-1}): 1646 (N−C═O). MS (EI, 70 eV), *m*/*z* (rel intensity): 278 (9), 277 (M$^+$, 51), 234 (22), 221 (23), 220 (100), 193 (11), 192 (54), 179 (25), 166 (7), 110 (10), 109 (6), 98 (5), 97 (27), 96 (8), 95 (10), 94 (18), 91 (11), 83 (14), 81 (20), 79 (14), 77 (8), 67 (14), 55 (11), 43 (34), 41 (22), 39 (11), 30 (8), 28 (10). ^{1}H NMR: 4.40 (d, ^3J = 4.9, H-8); 3.89 (d, ^2J = 15.2, H-2A); 3.62 (d, ^2J = 15.2, H-2B); 3.31 (d, ^3J = 3.6, H-9); 3.20 (d, ^3J = 3.6, H-11); 2.13 (s, $NCOCH_3$); 1.84 (m, H-5A); 1.79 (m, H-6); 1.73 (dd, ^2J = 12.0, ^3J = 8.0, H-7A), 1.42 (m, ^2J = 12.0, ^3J = 4.9, 3.7, H-7B); 1.38 (m, H-5B); 1.33 and 2.69 (2H, m, H-2′); 1.26 and 2.76 (2H, m, H-6′); 1.50−1.25 (6H, m, H-3′, H-4′, H-5′). ^{13}C NMR: 171.9 (NCO); 81.8 (C_1); 60.3 (C_4); 74.2 (C_8, J = 164.0); 51.2 (C_{11}, J = 192.3); 50.6 (C_9, J = 191.5), 43.4 (C_2, J = 138.3); 36.2 (C_5, J = 129.2); 34.7 (C_6, J = 132.0); 34.6 (C_7, J = 134.0); 34.1 ($C_{2'}$); 30.0 ($C_{6'}$); 25.7 ($NCOCH_3$, J = 128.3); 22.2, 22.4, 25.2 ($C_{3'}$, $C_{4'}$, $C_{5'}$). Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.31; H, 8.30; N, 5.05. Found: C, 69.28; H, 8.31; N, 5.00.

3-Acetylspiro[3-aza-10,12-dioxatetracyclo[6.3.1.0^{1,6}.0^{9,11}]-dodecane-4,1′-cycloheptane] (12b). The method was analogous to the synthesis of **12a**. Compound **12b**. White crystals. Mp: 163−164.5 °C (hexane−chloroform). R_f: 0.20 (ethyl acetate−hexane, 5:1). Yield: 92%. IR (ν, cm^{-1}): 1640 (N−C═O). MS (EI, 70 eV) *m*/*z* (rel intensity): 292 (5), 291 (M$^+$, 48), 276 (10), 262 (6), 248 (21), 234 (19), 221 (26), 220 (100), 193 (11), 192 (56), 179 (33), 97 (27), 95 (11), 94 (23), 91 (11), 83 (18), 79 (11), 67 (16), 55 (11), 43 (25). ^{1}H NMR (200 MHz, $CDCl_3$): 4.45 (d, ^3J = 4.8, H-8); 4.03 (d, ^2J = 15.0, H-2A); 3.37 (d, ^2J = 15.0, H-2B); 3.38 (d, ^3J = 3.6, H-9); 3.31 (d, ^3J = 3.6, H-11); 2.16 (s, $NCOCH_3$); 1.45 (m, H-7B); 2.70−2.40 (2H, m, H-2′); 2.1−1.1 (14H, m, H-3′, H-4′, H-5′, H-6′, H-7A, H-6, H-5). Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.10; H, 8.59; N, 4.81. Found: C, 70.05; H, 8.61; N, 4.72.

3-Acetyl-9,11-diacetoxyspiro[3-aza-10-oxatricyclo-[6.2.1.0^{1,6}]undecane-4,1′-cyclohexane] (13a) and 5-Acetyl-10-acetoxyspiro[5-aza-2-oxatricylo[6.2.1.0^{3,9}]undec-3-ene-6,1′-cyclohexane] (14a). BF_3·OEt_2 (7.4 mL, 58.6 mmol) was added to solution of 6.50 g (23.4 mmol) of compound **12a** in 80 mL of acetic anhydride with ice cooling. The mixture was stirred at 2−4 °C during 1 h (monitoring by TLC). At the end of the reaction, the mixture was diluted with water (300 mL), and concentrated ammonium hydroxide solution was added to pH 10−11. Three 100 mL extractions with ether were performed. The organic layers were combined and dried over $MgSO_4$. After solvent distillation, the reaction mixture was chromatographed on Al_2O_3 (20 × 3 cm, ethyl acetate−hexane, 1:20). In consecutive order isolated:

(1) Compound **13a**. Yield: 4.50 g (11.87 mmol). White needle-shaped crystals. Mp: 165.5−167 °C (hexane−ethyl acetate). R_f: 0.33 (ethyl acetate−hexane, 2:1). Yield: 50%. IR (ν, cm^{-1}): 1650 (N−C═O), 1730 (O−C═O). MS (EI, 70 eV) *m*/*z* (rel intensity): 379 (M$^+$, 2), 322 (7), 260 (8), 200 (3), 171 (5), 140 (5), 138 (8), 110 (6), 94 (5), 81 (5), 79 (6), 67 (7), 55 (6), 43 (100), 41 (7). ^{1}H NMR: 5.58 (s, H-9); 4.38 (d, ^3J = 1.7, H-11); 3.64 (d, ^2J = 14.4, H-2A); 3.13 (d, ^2J = 14.4, H-2B); 2.54 (dd, ^3J = 4.8, 1.7, H-8); 1.71 (m, H-6); 1.96 (s, $NCOCH_3$); 1.86 (s, $OCOCH_3$); 1.75 (s, $OCOCH_3$); 1.65 (m, ^2J = 12.5, ^3J = 10.7, 4.8, H-7B); 1.52 (dd, ^2J = 13.1, ^3J = 12.5, H-5B); 1.34 (dd, ^2J = 13.1, ^3J = 4.2, H-5A); 0.65 (dd, ^2J = 12.5, ^3J = 5.0, H-7A); 0.94 and 1.92 (2H, m, H-2′); 1.19 and 3.27 (2H, m, H-6′); 1.45−1.15 (6H, m, H-3′, H-4′, H-5′). ^{13}C NMR: 173.7 (NCO); 170.8 (OCO); 169.5 (OCO), 98.8 (C_9, J = 180.8); 84.2 (C_1); 77.1 (C_{11}, J = 158.7); 60.9 (C_4); 45.5 (C_2, J = 138.8); 45.0 (C_8, J = 153.6); 37.6 ($C_{6'}$); 35.3 (C_5, J = 127.5); 33.9 (C_6); 32.0 ($C_{2'}$); 27.0 (C_7, J = 135.8); 26.5 ($NCOCH_3$, J = 128.3); 22.2, 23.3, 26.0 ($C_{3'}$, $C_{4'}$, $C_{5'}$); 21.3 ($OCOCH_3$, J = 129.8); 20.9 ($OCOCH_3$, J = 130.0). Anal. Calcd for $C_{20}H_{29}NO_6$: C, 63.35; H, 7.66; N, 3.64. Found: C, 63.25; H, 7.61; N, 3.66.

(2) Compound **14a**. Yield: 3.41 g (10.65 mmol). Colorless crystals. Mp: 135.5−136.5 °C (hexane−ethyl acetate). R_f: 0.46 (ethyl acetate−hexane, 2:1). Yield: 45%. IR (ν, cm^{-1}): 1648 (N−C═O), 1682 (C═C), 1728 (O−C═O). MS (EI, 70 eV) *m*/*z* (rel intensity): 319 (M$^+$, 3), 276 (1), 259 (1), 234 (1), 205 (3), 182 (5), 138 (10), 120 (14), 96 (13), 81 (8), 67 (8), 55 (9), 43 (100), 41 (14). ^{1}H NMR: 5.66 (s, H-4); 4.70 (s, H-10); 4.56 (m, ^3J = 2.0, 1.1, H-1); 3.21 (d, ^3J = 4.0, H-9); 2.63 (dd, ^2J = 15.2, $_3J$ = 7.2, H-7A), 2.21 (m, H-8); 2.06 (m, ^2J = 14.0, ^3J = 9.4, 2.0, H-11A); 2.05 (s, $NCOCH_3$); 2.01 (s, $OCOCH_3$); 1.60 and 3.04 (2H, m, H-2′); 1.23 (ddd, ^2J = 14.0, ^3J = 3.0, 1.1, H-11B); 1.04 (m, ^2J = 15.2, ^3J = 8.4, ^4J = 2.4, H-7B); 1.12 and 2.74 (2H, m, H-6′); 1.7−1.1 (6H, m, H-3′, H-4′, H-5′). ^{13}C NMR: 172.8 (NCO); 170.7 (OCO); 154.0 (C_3); 103.6 (C_4, J = 182.3); 82.1 (C_1, J = 168.7); 76.0 (C_{10}, J = 159.5); 64.7 (C_6); 45.3 (C_9, J = 157.0); 37.9 (C_7); 36.6 (C_{11}); 33.5 ($C_{2'}$); 28.0 ($C_{6'}$); 26.5 ($NCOCH_3$, J = 128.0); 24.2 (C_8); 23.6, 24.1, 24.6 ($C_{3'}$, $C_{4'}$, $C_{5'}$); 20.8 ($OCOCH_3$, J = 130.0). Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.71; H, 7.83; N, 4.38. Found: C, 67.59; H, 7.90; N, 4.40.

3-Acetyl-9,11-diacetoxyspiro[3-aza-10-oxatricyclo-[6.2.1.0^{1,6}]undecane-4,1′-cycloheptane] (13b) and 5-Acetyl-10-acetoxyspiro[5-aza-2-oxatricyclo[6.2.1.0^{3,9}]undec-3-ene-6,1′-cycloheptane] (14b). The method was analogous to the synthesis of **14a** and **14b**. From reaction with 1.00 g (3.43 mmol) compound **12b** were isolated:

(1) Compound **13b**. Yield: 0.60 g (1.54 mmol). White needle-shaped crystals. Mp: 141.5−143 °C (hexane−ethyl acetate); R_f: 0.14 (ethyl acetate−hexane, 1:1). Yield: 45%. IR (ν, cm^{-1}): 1649 (N−C═O), 1737 (O−C═O). MS (EI, 70 eV) *m*/*z* (rel intensity): 393 (M$^+$, 16), 334 (18), 323 (24), 322 (92), 294 (12), 274 (43), 232 (19), 202 (13), 185 (15), 180 (11), 154 (16), 138 (13), 95 (12), 94 (15), 93 (13), 91 (16), 81 (11), 79 (15), 67 (17), 60 (11), 55 (11), 45 (10), 44 (11), 43 (100), 42 (11). ^{1}H NMR:

5.79 (s, H-9); 4.64 (d, ^3J = 1.7, H-9); 3.85 (d, ^2J = 13.9, H-2B); 3.30 (d, ^2J = 13.9, H-2A); 2.91 (m, H-2′A); 2.77 (dd, ^3J = 4.8, 1.7, H-8); 2.11 (s, $OCOCH_3$); 2.09 (s, $NCOCH_3$); 2.06 (m, ^2J = 13.1, ^3J = 10.5, 4.8, H-7B); 2.03 (s, $OCOCH_3$); 1.91 (m, H-6); 1.80 (dd, ^2J = 13.6, ^3J = 4.0, H-5B); 1.63 (dd, ^2J = 13.6, ^3J = 13.0, H-5A); 1.38 (m, H-2′B); 0.99 (dd, ^2J = 13.1, ^3J = 5.5, H-7A); 1.9−1.1 (10H, m, H-3′, H-4′, H-5′, H-6′, H-7′). ^{13}C NMR: 172.6 (NCO); 170.7 (OCO); 169.5 (OCO); 98.5 (C_9); 82.6 (C_1); 77.2 (C_{11}); 64.2 (C_4); 46.1 (C_2); 44.7 (C_8); 42.7 ($C_{2'}$); 36.8 (C_5); 33.4 (C_6); 26.7 (C_7); 26.2 ($NCOCH_3$); 21.2 ($OCOCH_3$); 20.8 ($OCOCH_3$); 30.1, 24.9, 23.7, 29.7, 31.3 (C_3, C_4, C_5, C_6, C_7). Anal. Calcd for $C_{21}H_{31}NO_6$: C, 64.12; H, 7.88; N, 3.56. Found: C, 64.00; H, 7.93; N, 3.53.

(2) Compound **14b**. Yield: 0.34 g (1.02 mmol). White needle-shaped crystals. Mp: 151.5−153 °C (hexane−ethyl acetate). R_f: 0.44 (ethyl acetate−hexane, 1:1). Yield: 30%. IR (ν, cm^{-1}): 1648 (N−C=O), 1689 (C=C), 1733 (O-C=O). MS (EI, 70 eV), *m*/*z* (rel intensity): 333 (M^+, 17), 201 (9), 196 (12), 181 (11), 168 (15), 140 (14), 138 (34), 134 (36), 96 (45), 93 (14), 92 (15), 91 (22), 83 (14), 81 (15), 79 (20), 77 (12), 67 (28), 66 (10), 55 (17), 53 (10), 43 (100). ^{1}H NMR: 5.62 (s, H-4); 4.69 (s, H-10); 4.55 (d, ^3J = 1.8, H-1); 3.14 (d, ^3J = 3.9, H-9); 2.62 (m, H-7′A); 2.59 (m, H-2′A); 2.39 (dd, ^2J = 14.3, ^3J = 7.5, H-7A); 2.30 (m, H-8); 2.06 (m, ^2J = 14.1, ^3J = 9.5, 1.8, H-11B); 2.04 (s, $NCOCH_3$); 1.98 (s, $OCOCH_3$); 1.65 (m, H-7′B); 1.23 (dd, ^2J = 14.1, ^3J = 3.5, H-11A); 1.15 (m, H-2′B); 1.14 (dd, ^2J = 14.3, ^3J = 7.7, H-7B); 2.0−1.2 (8H, m, H-3′, H-4′, H-5′, H-6′). ^{13}C NMR: 172.4 (NCO); 170.6 (OCO); 169.5 (OCO); 154.0 (C_3); 103.1 (C_4, J = 182.3); 82.1 (C_1, J = 168.5); 76.0 (C_{10}, J = 158.7); 67.3 (C_6); 45.8 (C_9, J = 156.5); 43.8 (C_7); 39.3 ($C_{2'}$); 36.4 (C_{11}); 25.9 ($NCOCH_3$, J = 128.2); 24.6 (C_8); 20.7 ($OCOCH_3$, J = 129.9); 24.5, 29.5, 29.5, 25.1, 35.7 ($C_{3'}$, $C_{4'}$, $C_{5'}$, $C_{6'}$, $C_{7'}$). Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.46; H, 8.10; N, 4.20. Found: C, 68.48; H, 8.11; N, 4.19.

5-Acetyl-4,10-dibromospiro[5-aza-2-oxatricyclo[6.2.1.0^{3,9}]-undec-3-ene-6,1′-cyclohexane] (15). NBS 0.66 g (3.80 mmol) and catalytic amounts of *m*-chloroperbenzoic acid were added to solution of 0.50 g (1.90 mmol) of compound **10** in 25 mL of chloroform. The reaction mixture was boiled for 2.5 h. Then it was diluted with water (50 mL), extracted with ether (5 × 20 mL), and dried over $MgSO_4$. After solvent distillation, the mixture was purified on aluminum oxide (1 × 10 cm, ethyl acetate−hexane, 1:10). Colorless crystals (0.25 g, 0.59 mmol) of compound **15** were isolated. Mp: 155 °C dec. R_f: 0.71 (ethyl acetate−hexane, 1:1). Yield: 30%. IR (ν, cm^{-1}): 1661 (N−C=O), 1694 (C=C). MS (EI, 70 eV) *m*/*z* (rel intensity): 421 (M^+, 3 for Br^{81}), 419 (6), 417 (3), 377 (2), 340 (12), 298 (13), 296 (15), 269 (11), 216 (20), 199 (13), 189 (10), 176 (20), 174 (20), 140 (11), 138 (100), 121 (23), 96 (18), 95 (11), 94 (10), 93 (10), 91 (12), 82 (12), 81 (20), 80 (12), 79 (20), 77 (10), 67 (16), 66 (13), 65 (10), 43 (46). ^{1}H NMR: 4.68 (q, ^3J = 1.3, 1.3, ^4J = 1.3, H-1); 3.99 (d, ^3J = 1.3, H-10); 3.38 (m, ^3J = 4.0, 1.3, ^4J = 1.3, H-9); 2.97 (m, H-6′A); 2.75 (dd, ^2J = 15.5, ^3J = 6.6, H-7A); 2.64 (m, H-2′A); 2.24 (m, H-8); 2.23 (s, $NCOCH_3$); 2.14 (m, ^2J = 13.6, ^3J = 9.6, 1.6, H-11B); 1.53 (m, H-6′B); 1.45 (m, H-2′B); 1.44 (m, ^2J = 13.6, ^3J = 2.8, ∼1.0, H-11A); 0.99 (m, ^2J = 15.5, ^3J = 8.8, ^4J = 2.4, H-7B); 1.7−1.2 (6H, m, H-3′, H-4′, H-5′). ^{13}C NMR: 173.9 (NCO); 154.2 (C_3); 93.1 (C_4); 85.5 (C_1, J = 173.2); 66.3 (C_6); 52.7 (C_9, J = 158.6); 49.3 (C_{10}, J = 163.2); 38.1 (C_7); 37.5 (C_{11}); 33.3 ($C_{2'}$); 28.2 (C_8); 27.7 ($C_{6'}$); 26.5 ($NCOCH_3$, J = 129.0); 23.3, 24.4, 24.6 ($C_{3'}$, $C_{4'}$, $C_{5'}$). Anal. Calcd for $C_{16}H_{21}NO_2Br_2$: C, 45.85; H, 5.05; N, 3.34; Br, 38.13. Found: C, 45.55; H, 5.37; N, 3.33; Br, 38.59.

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Supporting Information Available: Complete crystallographic data for structures **14a** and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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