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Chemistry of 3-Azabicyclo[3.3.1]nonane: II.* Reduction of 6-Acetoxy-3-benzyl-1-ethoxycarbonyl-3-azabicyclo[3.3.1]nonan-9-one with Sodium Borohydride

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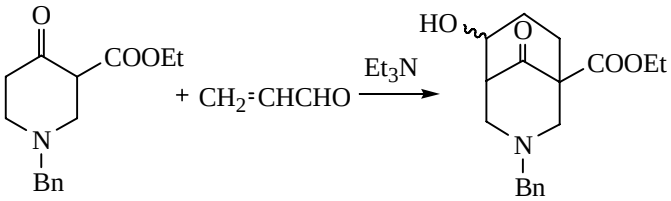
Abstract—Reduction of 6-acetoxy-3-benzyl-1-ethoxycarbonyl-3-azabicyclo[3.3.1]nonan-9-one with sodium borohydride was investigated in various conditions. The stereochemistry of reduction products was deduces from ^{1}H and ^{13}C NMR and mass spectra.

3-Azabicyclo[3.3.1]nonane system is an important structural moiety ensuring the high physiological activity (antiarrythmic, spasmolytic, psychotropic, curarelike etc) of diterpene alkaloids [2]. The purposeful transformation of diterpene alkaloids led to preparation of a number of compounds exceeding the known antiarrythmic drugs in activity and antiarrythmic index and favorably differing from the former by the absence of inotropic effect and no effect on the blood pressure in the theurapeutic doses. The published reports on the synthesis of the above mentioned azabicyclononane systems concern as a rule either nonfunctionalized substances or those with a small number of oxygen-containing groups.

We showed formerly that the reaction of 1-benzyl-3-methoxycarbonyl-4-piperidone with acrolein catalyzed by triethylamine afforded 3-benzyl-6-hydroxy-1-methoxycarbonyl-3-azabicyclo[3.3.1]nonan-9-ones as epimeric alcohols in a ratio 1:4 (equatorial alcohol prevailing) [1]. The reaction with 1-benzyl-3-ethoxy-carbonyl-4-piperidone occurred with higher stereoselectivity (the ratio of epimeric alcohols **Ia** and **If** was 1:12; *a* corresponded to the axially oriented hydroxy group, and e to the equatorial one). The isomeric ratio **Ia** and **If** was estimated from



Ia, If

Reaction conditions and products obtained by reduction with sodium borohydride of 6-acetoxy-3-benzyl-1-ethoxycarbonyl-3-azabicyclo[3.3.1]nonane-9-one

Run no.	Reaction conditions[a]	Reaction products	Conversion of initial ketone, %
1	$NaBH_4$, MeOH, 18 h	**α-IIIf, β-IIIf, β-IIIa**	100[b]
2	$NaBH_4$, MeOH + H_2O (50:3), 18 h	**α-IIIε, β-IIIf, α-IIIa, β-IIIa**	100
3	2 mol $NaBH_4$, MeOH + H_2O (50:3), 18 h	**α-IIIf, β-IIIf, β-IIIa, α-IVf, β-IVf**	100
4	$NaBH_4$, MeOH + H_2O (4:1), 18 h	**α-IIIε, β-IIIf, β-IVf**	100
5	$NaBH_4$, *i*-PrOH, 18 h	**α-IIIf, β-IIIf, α-IVf, β-IVf**	100
6	$NaBH_4$–$NiCl_2$, THF, 50°C, 20 min	**α-IIIf, β-IIIf, α-IVf, β-IVf**	40–50[c]
7	$NaBH_4$–$CeCl_3$, MeOH, 30 min	**α-IIIf, β-IIIf, β-IIIa**	20
8	2 mol $NaBH_4$–1 mol $CeCl_3$, MeOH + H_2O, 18 h	**α-IIIf, β-IIIf, α-IIIa, β-IIIa**	100

[a] All runs except for run no.6 were performed at room temperature.

[b] No signals of initial ketone appeared in the ^{13}C NMR spectra of the reaction mixture; in all cases the yield of reaction products exceeded 90%.

[c] Alongside the reduction products formed up to 10–15% of product resulting from ring opening at the C^5 atom.

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the intensity of signals from C^6 β atoms in the ^{13}C NMR spectrum (with an error ≈10%) [1] for in the ^1H NMR spectrum in the region 4.0–4.15 ppm the signal of the axial proton linked to C^6 was overlapped by the resonance of the CH_2 group of the ethyl substituent. At the use of potassium carbonate as alternative catalyst the expected inversion in the reaction selectivity observed in the case of 1-benzyl-3-methoxycarbonyl-4-piperidone did not occur: On the contrary, the stereoselectivity of the reaction was reduced (the ratio of **a** and **e** isomers became ≈1:1.2).

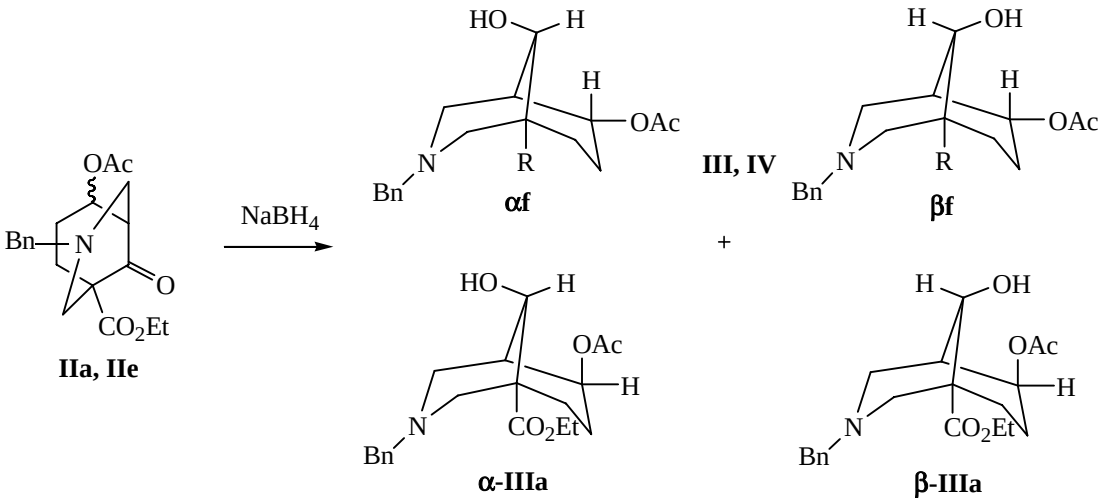
We chose as an object of investigation acetate **IIa, IIf** for with this compound the ^1H and ^{13}C NMR spectra possessed less complicated pattern. Acetate **IIa, IIf** was prepared by a standard procedure in a 92% yield from the isomeric mixture of compounds **Ia, If** synthesized using triethylamine as catalyst. The isomeric ratio of acetates was the same as that of alcohols.

We studied the stereoselectivity of 6-acetoxy-3-benzyl-1-ethoxycarbonyl-3-azabicyclo[3.3.1]nonan-9-one (**IIa, IIf**) reduction with sodium borohydride. The reaction was carried out under variable conditions (changing the solvent, temperature, reagents ratio, introducing stereocontrolling additives). The composition of alcohols obtained depending on the reaction conditions is presented in the table. In all cases save those specially indicated the ratio substrate–$NaBH_4$–additive was 1:1:1.

The ratio of α- and β-epimeric alcohols formed from each isomer was approximately the same in all cases and equal to 2 : 3 . The prevalence in all cases of the β-epimer alcohol is well consistent with the published data [3]. The attempts to affect the stereoselectivity of the reduction with $NiCl_2$ [4] or $CeCl_3$ [5] additives were unsuccessful. The double increase in the molar ratio of $NaBH_4$ to the substrate in the presence of $CeCl_3$ (see table, run no. *8*) resulted in higher conversion of the initial ketone.

In some cases alongside the products **III** originating from reduction of group C^9=O an additional reduction occurred of the C^1-ethoxycarbonyl group furnishing an epimeric mixture of an equatorial isomer of diol **α,β-(IVf)**. For instance, twice increased molar amount of $NaBH_4$ (in a mixed solvent MeOH–water, 50:3 [6]) resulted in additional formation of two diol **IVf** epimers [the ratio **β-(IIIa, IIIf)/α,β-(IVf)** = 3:1, the ratio **α:β** = 2:3]. The raising of the molar ratio substrate–$NaBH_4$ to 1:3 (in the same solvent system) did not significantly increse the diol yield. The larger content of water in the MeOH–water mixture (to the ratio 4:1) at the equimolar ratio substrate–$NaBH_4$ favored alongside formation of the reduction products at the C^9 atom also β-epimer of diol **IVf**. The change of the solvent for *i*-PrOH at the equimolar ratio substrate–$NaBH_4$ also resulted in formation of a small amount of the epimeric mixture of diols **α,β-(IVf)**. The reaction carried out in the presence of $NiCl_2$ additive at heating to 50°C in THF gave rise not only to the products of reduction of the C^9=O group and epimeric mixture of diol **IV** but also to the compound arising by ring opening at the C^5 atom (see table, run no. *6*).

The structures of compounds synthesized were established from ^1H and ^{13}C, CH-Corr NMR, and mass spectra.



R = CO_2Et (**III**), CH_2OH (**IV**).

The ratio of α,β-epimeric alcohols was estimated by the integral intensity of the singlet signals of O-acetyl groups attached to C^6 atoms in the ^1H NMR spectra. The most characteristic signals in the carbon spectra of the reduction products are the downfield signals of C^6 atom (δ 70.30–73.42 ppm), of atom C^9 (δ 68.54–77.20 ppm), and of $\underline{CH_2}$Ph group (δ 62.02–68.99 ppm). The assignment of signals belonging to alcohols **α,β-(IIIa, IIIf)** was performed, firstly, by the intensity of the signals from the mentioned groups (isomer ratio 1:12), and secondly, by comparison with the signals of the initial acetate **IIa, f** and with those of diol **α,β-(IVf)** isolated in an individual state. According to calculated [7] and also published data [3, 8, 9] the upfield signal of C^9 atom, δ 77.20 ppm, corresponds to the α-epimer, and the downfield signal, δ 68.54 ppm, to the β-epimer of the prevailing isomer **IIIf** whereas the signals at δ 73.22 (**α**) and 71.37 (**β**) ppm respectively belong to the minor isomer **III*a***.

The epimeric mixture of the equatorial isomer of diol **α,β-(IVf)** was isolated by column chromatography on Al_2O_3. In the ^1H NMR spectrum of this pair of epimeric alcohols the proton signals in position *6* have identical splitting pattern (d.d.d) due to coupling with two protons attached to C^7 and on a proton at C^5; the coupling constants in both isomers are virtually equal. Thus the acetoxy group in position *6* in both isomers is identically (equatorially) located. In the ^1H NMR spectrum appear two new signals from protons at the hydroxy group in position *9* (δ 3.71 and 3.94 ppm) corresponding to *exo*- and *endo*-isomers (or to α and β respectively). The isomer ratio **α:β** = 2:3. The doublet from the prevailing isomer appears upfield and corresponds to the *endo*-isomer [3, 7, 8]. In the ^{13}C NMR spectrum, as shown by the CH-Corr spectrum, the chemical shifts of the carbon atoms of the *endo*-isomer equal to δ 70.82 (C^9) and 73.63 (C^6) ppm, and those of *exo*-isomer to 74.81 (C^9) and 71.62 (C^6) ppm.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were registered on a spectrometer Bruker AMXIII-300 (operating frequencies 300.13 and 75.47 MHz respectively) from 1–3% and 10–20% solutions in $CDCl_3$, internal reference TMS. IR spectra were recorded on a spectrophotometer Specord from thin films or ftom mulls in mineral oil. Mass spectra were measured on MKh-1306 instrument at ionizing voltage 70 V and ionizing chamber temperature 150–200°C.

The reaction progress was monitored by TLC on Sorbfil PTSKh AF-A plates (Krasnodar). Individual compounds were isolated by column chromatography on neutral aluminum oxide. The eluents used were either chloroform or solvent system chloroform–methanol (100:1, 50:1, 25:1, 10:1).

3-Benzyl-6-hydroxy-1-ethoxycarbonyl-3-azabicyclo[3.3.1]nonan-9-ones (I*a*, f) were prepared along previously described procedure [1]. *a*. Catalyst Et_3N, yield 96.7%. IR spectrum, cm^{-1}: 508, 574, 610, 664, 688, 706, 742, 796, 862, 916, 952, 1012, 1054, 1096, 1138, 1168, 1192, 1252, 1342, 1378, 1444, 1480, 1720, 2968, 3412. Isomer ratio ***a*:f** ≈ 1:12. Prevailing isomer **(If)**. ^{13}C NMR spectrum, δ, ppm: 13.83 q (Me in Et), 29.68 t (C^8), 30.10 t (C^7), 53.89 t (C^4), 54.22 d (C^5), 57.73 s (C^1), 60.83 t (C^2), 61.03 t (CH_2 in Et), 61.51 t ($\underline{CH_2}$Ph), 72.14 d (C^6), 127.12–128.43 d, 137.68 s (Ph), 170.44 s (COO), 209.23 s (C=O).

Isomer Ia. ^{13}C NMR spectrum, δ, ppm: 14.01 q (Me in Et), 29.02 t (C^8), 31.62 t (C^7), 54.24 d (C^5), 56.49 t (C^4), 58.08 C (C^1), 58.66 t (C^2), 60.95 t (CH_2 in Et), 61.59 t ($\underline{CH_2}$Ph), 76.19 d (C^6), 127.31–128.73 d, 137.86 s (Ph), 171.02 s (COO), 210.42 s (C=O).

b. Catalyst K_2CO_3, yield 82.6%. Isomer ratio ***a*:f** ≈ 1.2:1.

6-Acetoxy-3-benzyl-1-ethoxycarbonyl-3-azabicyclo[3.3.1]nonane-9-ones (II*a*, f) were prepared by a standard procedure in a 92% yield from an isomer mixture **Ia, If** obtained along method *a*. Isomer ratio remained unchanged. IR spectrum, cm^{-1}: 604, 700, 748, 784. 916, 958, 1030, 1054, 1072, 1108, 1156, 1180, 1234, 1264, 1366, 1456, 1492, 1738, 2932. Prevailing isomer **(IIf).** Characteristic signals in ^1H NMR spectrum, δ, ppm: 1.27 t (3H, $CH_2\underline{Me}$, *J* 7.14 Hz), 2.02 s (3H, CO$\underline{Me}$), 2.55 m (1H, H^5), 4.19, 4.24 d.d (2H, $\underline{CH_2}$Me, *J* –14.27, 7.14 Hz), 5.12 m (1H, H^{6a}), 7.30 m (5H, Ph). ^{13}C NMR spectrum, δ, ppm: 13.93 q ($CH_2\underline{Me}$), 20.83 q (CO$\underline{Me}$), 26.51 t (C^8), 30.03 t (C^7), 51.25 d (C^5), 54.34 t (C^4), 57.94 t (C^2), 58.18 C (C^1), 61.21 t ($\underline{CH_2}$Ph), 61.47 t ($\underline{CH_2}$Me), 73.22 d (C^6), 127.17 d, 128.08 d, 128.43 d, 137.70 s (Ph), 169.56 s (COO), 170.01 s (OCO), 207.13 s (C=O).

Isomer **(II*a*)**. Characteristic signals in ^1H NMR spectrum, δ, ppm: 1.20 t (3H, $CH_2\underline{Me}$), 2.04 s (3H, CO$\underline{Me}$), 5.35 br.s (1H, H^{6e}). Characteristic signals in ^{13}C NMR spectrum, δ, ppm: 21.00 q (CO$\underline{Me}$), 51.39 d (C^5), 61.76 t ($\underline{CH_2}$Me), 78.00 d (C^6), 127.33–128.71 d, 138.22 s (Ph), 208.61 s (C=O).

6-Acetoxy-3-benzyl-9-hydroxy-1-ethoxycarbonyl-3-azabicyclo[3.3.1]nonanes α,β-(IIIa, IIIf). To

0.54 g of acetate **IIa, IIf** in a mixture of 22.6 ml of MeOH and 1.33 ml of water was added 0.315 g of $NaBH_4$ [4]. The stirring at room temperature continued for 18 h. On cooling glacial acetic acid was added to the reaction mixture till pH ~5, then the solvent was distilled off at reduced pressure, water was added to the residue, and the reaction products were extracted into chloroform.. Yield 0.5 g (92.6%). The ratio of epimeric alcohols **α:β** = 2:3. IR spectrum, cm^{-1}: 610, 670, 706, 760, 904, 1012, 1036, 1108, 1234, 1324, 1348, 1420, 1438, 1480, 1720, 2914, 3436.

β-Epimer of prevailing isomer **(IIIf)**. ^{13}C NMR spectrum, δ, ppm: 13.67 q (Me in Et), 20.98 q (Me in AC), 29.36 t (C^7), 30.63 t (C^8), 39.24 d (C^5), 46.42 t (C^2), 47.18 C (C^1), 53.21 t (C^4), 59.51 t ($\underline{CH_2}$Me), 62.71 t ($\underline{CH_2}$Ph), 68.65 d (C^9), 72.89 d (C^6), 126.40–128.17 d, 138.41 s (Ph), 170.00 s (OCO), 175.55 s (COO).

α-Epimer of prevailing isomer **(IIIf)**. ^{13}C NMR spectrum, δ, ppm: 13.77 q (Me in Et), 20.68 q (Me in AC), 25.89 t (C^7), 26.64 t (C^8), 38.23 d (C^5), 45.99 t (C^4), 47.18 C (C^1), 52.19 t (C^2), 59.51 t ($\underline{CH_2}$Me), 62.02 t ($\underline{CH_2}$Ph), 70.41 d (C^9), 77.20 d (C^6), 126.40–128.17 d, 137.96 s (Ph), 170.12 s (OCO), 175.50 s (COO).

β-Epimer of minor isomer **(III*a*)**. ^{13}C NMR spectrum, δ, ppm: 21.13 q (Me β AC), 29.04 t (C^7), 31.60 t (C^8), 38.59 d (C^5), 46.22 t (C^4), 47.07 s (C^1), 53.33 t (C^2), 60.64 t ($\underline{CH_2}$Me), 62.54 t ($\underline{CH_2}$Ph), 71.47 d (C^9), 72.59 d (C^6), 126.40–128.17 d, 137.63 s (Ph), 169.37 s (OCO), 175.05 s (COO).

α-Epimer of minor isomer **(III*a*)**. ^{13}C NMR spectrum, δ, ppm: 21.06 q (Me β AC), 47.00 s (C^1), 60.52 t ($\underline{CH_2}$Me), 62.02 t ($\underline{CH_2}$Ph), 73.57 d (C^6), 126.40–128.17 d, 138.65 s (Ph).

6-Acetoxy-3-benzyl-9-hydroxy-1-(hydroxymethyl)-3-azabicyclo[3.3.1]nonanes α,β-(IVf). The ratio of epimeric alcohols **α:β** = 2:3. IR spectrum, cm^{-1}: 700, 754, 910, 1024, 1066, 1246, 1366, 1450, 1492, 1732, 2920, 3394. M^+ 319.18. $C_{18}H_{25}NO_4$. **β-Epimer.** ^1H NMR spectrum, δ, ppm: 1.30 m (1H, H^{8e}), 1.47 m (1H, H^{8a}), 1.60 br.s (1H, OH), 1.88 m (1H, H^{7e}), 2.02 s (3H, AC), 2.17 br.s (1H, H^5), 2.42 d (1H, H^2, *J* 11.2 Hz), 2.52 d.d (1H, H^4, *J* 11.7, 3.7 Hz), 2.62 d (1H, H^2, *J* 11.2 Hz), 2.73–2.86 m (2H, $H^{4,7a}$), 3.38 d, 3.55 d (2H, $\underline{CH_2}$Ph, *J* 13.3 Hz), 3.69 d (1H, H^9, *J* 3.1 Hz), 4.92 m (1H, H^{6a}), 7.30 m (5H, Ph). ^{13}C NMR spectrum, δ, ppm: 21.02 q (Me in AC), 26.37 t (C^7), 29.81 t (C^8), 38.39 s (C^1), 40.23 d (C^5), 46.62 t (C^4), 54.45 t (C^2), 62.95 t ($\underline{CH_2}$OH), 68.99 t ($\underline{CH_2}$Ph), 70.82 d (C^9), 73.63 d (C^6), 126.45–129.48 d, 138.76 s (Ph), 170.62 s ($\underline{OCO}$Me).

α-Epimer. Characteristic signals in ^1H NMR spectrum, δ, ppm: 3.92 d (1H, H^9, *J* 3.5 Hz), 5.37 m (1H, H^{6a}). ^{13}C NMR spectrum, δ, ppm: 21.13 q (Me in AC), 25.55 t (C^7), 28.71 t (C^8), 37.75 C (C^1), 39.22 d (C^5), 52.36 t (C^4), 60.32 t (C^2), 62.50 t ($\underline{CH_2}$OH), 68.56 t ($\underline{CH_2}$Ph), 71.62 d (C^6), 74.81 d (C^9), 126.45–129.48 d, 137.95 s (Ph), 170.96 s ($\underline{OCO}$Me).

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