DIAZABICYCLOALKANES WITH BRIDGING NITROGEN ATOMS. 23.* SYNTHESIS AND PROPERTIES OF BENZO[f]-1,5-DIAZABICYCLO[3.2.2]NONEN-3-OL

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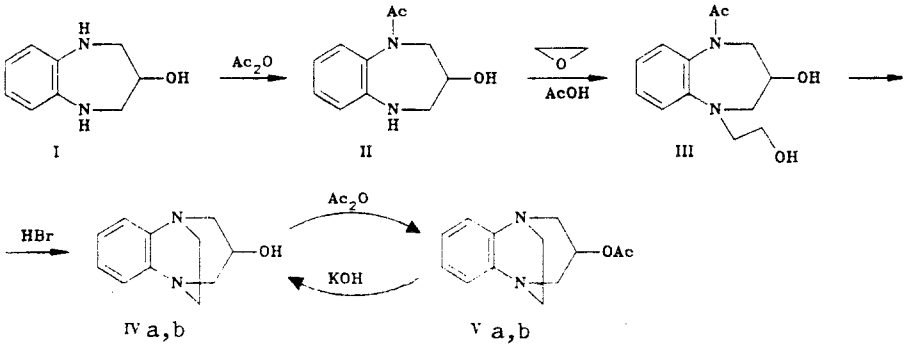
Intramolecular cyclization 1-(2-hydroxyethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-3-ol gives benzo[f]-1,5-diazabicyclo[3.2.2]nonen-3-ols. Further treatment with acetic anhydride gives their 3-acetyl derivatives. The stereoisomers have been separated and their substituent configurations shown by PMR spectroscopy.

The intramolecular cyclization in hydrobromic acid of the N-2-hydroxyethyl derivatives of 1,2,3,4-tetrahydroquinoxaline, N,N'-trimethylene- and N,N'-tetramethylene-o-phenylenediamines gives the corresponding benzodiazabicycloalkenes [2, 3]. Applying this approach, we have synthesized the first of the series derivatized in the alicyclic part of the molecule which are the benzo[f]-1,5-diazabicyclo[3.2.2]nonen-3-ols (IVa, b). We have studied some of their chemical properties.

The previously [4] reported 2,3,4,5-tetrahydro-1H,-1,5-benzodiazepin-3-ol (I) was used as starting material.



Acetic anhydride in ethanol was used to acetylate I in order to avoid O-acetylation. The acetyl compound II was obtained in high yield. Elemental analytical data and mass spectrometry showed only one acetyl group. The IR spectrum showed the presence of an amide absorption band at 1650 cm^{-1} and the absence of an ester band at 1710-1750 cm^{-1} pointing to the formation of the N-acetyl derivative. The PMR spectrum of II in $CDCl_3$ showed two sets of signals for two conformers associated with hindered rotation of the $COCH_3$ group around the amide C—N bond. This is confirmed by a study of the temperature dependence of the spectrum of II in $CHBr_3$. At 50°C broadening of the methyl group signals is observed (δ 2.025 and 1.925 ppm) and at 80°C full coalescence occurs. The ratio of conformers was ≃4:1. For the major conformer a full assignment of the PMR signals was carried out. the signals of the minor conformer were close in chemical shift to those of the major conformer; hence their correct assignment was difficult.

Treatment of II with ethylene oxide in acetic acid gives the N-2-hydroyethylene derivative III. By microcolumn HPLC it was shown that the hyroxyethylation goes in 80-85% yield. Compound III is obtained as an oil and has IR, PMR, and mass spectra in agreement with the proposed structure. We did not, however, achieve a satisfactory elemental analysis.

*For Communication 22 see [1].

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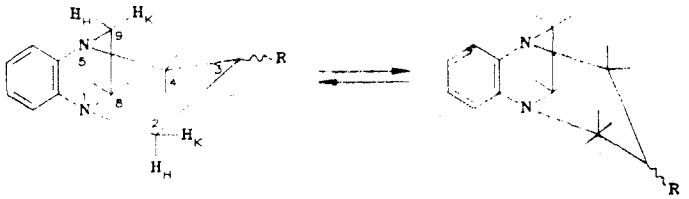
Compound III was subsequently cyclized without additional purification by refluxing in HBr. According to HPLC, the reaction mixture at 60-70% cyclization consisted of two isomers in similar amounts with identical UV spectra and similar retention times. They are shown to be the stereoisomers IVa and IVb, i.e., the cyclization occurs nonstereospecifically, as expected. The reaction mixture did not contain the products of exchange of the hydroxy group in IV for bromine. Because this exchange is extremely likely in the conditions of refluxing HBr, it can be inferred that this is the dominant indirect process.

Compound IV, like unsubstituted benzo[f]-1,5-diazabicyclo[3.2.2]nonene [3], was stable in HBr and does not form an equilibrium mixture with ring opened products as reported previously [2] for benzo[b]-1,4-diazabicyclo[2.2.2]octene.

Prolonged refluxing of a benzene solution of a mixture of IVa, b with excess acetic anhydride and base gives a mixture of the stereoisomers of benzo[f]-1,5-diazabicyclo[3.2.2]nonene-3-acetate (Va, b). This mixture was fractionally crystallized from hexane. Isomer Va occurs as fine needles with mp 139-140°C and Vb as prisms with mp 93-95°C. Alkaline hydrolysis of the separated Va and Vb gave the stereoisomers IVa and IVb.



The PMR spectra of solutions of the stereoisomers Va, Vb, IVa, and IVb (Table 1) show AA'BB' type aromatic proton signals at 7.1-7.2 ppm and multiplets at 3.7-3.4 and 3.2-3.1 ppm for atoms H_K and H_H of the 8- and 9-CH_2 groups. Assignment of the remaining protons was carried out by iterative calculation of the AA'BB'C type system. Based on the values of the vicinal spin—spin couplings and chemical shifts of the H_3 protons (cf. data for unsubstituted benzo[f]-1,5-diazabicyclo[3.2.2]nonene [1]) compound Va and hydrolysis product IVa were assigned the structures with substituents exo to the benzene ring whereas in Vb and hydrolysis product IVb the substituents are in the endo position. By comparing the H_2 to H_3 coupling constants for IVa, IVb, Va, and Vb with data for fixed conformations [1] it was shown that they were in rapid conformational exchange. In contrast to the previously synthesized benzodiazabicycloalkenes [3] the mass spectra of IVa, b and Va, b did not show characteristic ions for $[M-28]^+$ corresponding to the fission of ethylene fragments. The most intense peaks for compounds IVa, b and Va, b are a residual ion with mass 146 corresponding to fission of the fragment CH_2CHOR, where R = H, $COCH_3$.

Compounds IVa, b readily form quaternary ammonium salts. Treatment of an ether solution of IV with excess methyl iodide leads to almost immediate precipitation of clear crystals of benzo[f]-1,5-diazabicyclo[3.2.2]nonen-3-ol-1-methiodides (VI).

EXPERIMENTAL

IR spectra were recorded on a UR-20 spectrophotometer (KBr tablets), UV spectra on a Specord UV-vis (ethanol solvent), and PMR spectra on a Bruker WP-200 spectrometer. Mass spectra and molecular mass values were obtained on a Finnigan MAT-8200 instrument. Reaction mixtures were analyzed by TLC on Silufol UV-254 plates with the solvent systems: chloroform—ethanol, 10:1 (system A); tert-butanol-methylethylketone-formic acid—water 8:6:3:3 (system B), and microcolumn reversed phase liquid chromatography was performed on Nucleosil C-18 sorbent (5 μm). The column dimensions were 2 × 50 mm and the eluent 1.2 ml of a linear gradient from 30 to 50% of MeOH in 0.01 M Na_2HPO_4 (system C). The flow rate was 0.05 ml/min and the eluate was continuously analyzed on a Millichrom chromatograph using UV light at wavelength 210 and 250 nm. Before application to the column, the sample was neutralized to pH 7 with a solution of diisopropylethylamine—water—methanol 1.5:2.5:5.5.

Elemental analytical data for II, IV, Va, b, and VI agreed with those calculated.

1-Acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-3-ol (II). Acetic anhydride (6 ml, 60 mmoles) was added dropwise with stirring over 30 min to a suspension of 2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-3-ol (I) (9 g, 55 mmoles) [4] in ethanol (90 ml). After 1 day the solution was evaporated, the residue neutralized with aqueous Na_2CO_3, and extracted with $CHCl_3$ (4 × 50 ml). The yellow oil formed after filtration and evaporation of the combined chloroform extracts was crystallized from a mixture of petrol ether—ethyl acetate (1:1) to give 9.6 g (85%) of colorless crystals with mp 148-149°C ad R_f 0.3 (A). IR spectrum (in KBr): 1060 (C—N); 1320 (C—O stretching); 1505, 1610 (arom. C=C); 1650 (C=O); 2960 (CH_3 stretch); 3000-3070 (arom. C—H), 3280 (N—H), 3150-3400 cm^{-1} (O—H). UV spectrum (in ethanol), λ_{max}, nm (log ε): 217 (4.27), 241 (sh, 4.00), 292 (3.33). Mass spectrum, m/z (I, %): 206 (70) $[M]^+$, 177 (20) $[M - COH]^+$, 166 (22) $[M - COCH_3]^+$, 146 (16), 145 (22), 133 (13), 120 (28), 119 (100) $[M - CH_2CHOH + COCH_3]^+$. M 206.1047 (mass spectral). PMR spectrum (in $CDCl_3$): 6.70-7.20

TABLE 1. PMR Spectra of Compounds IV and V in $CDCl_3$

Compound	R	Chemical shift, δ, ppm						Spin-spin coupling, J, Hz		
		H_{arom} AA'BB'	$COCH_3$	H_{3H} (H_{3K})	H_{2H} = H_{4H}	H_{2K} = H_{4K}	$H_{8,9K}$ ($H_{8,9H}$)	$H_{2H}, H_{2K} = H_{4H}, H_{4K}$	$H_{3H}, H_{2K} = H_{3H}, H_{4K}$ ($H_{3K}, H_{2K} = H_{3K}, H_{4K}$)	$H_{3H}, H_{2H} = H_{3H}, H_{4H}$ ($H_{3K}, H_{2H} = H_{3K}, H_{4H}$)
Va	exo-OCOCH$_3$	7,06 ... 7,23	2,11	4,88	3,39	3,36	3,68 (3,22)	−15,16	3,91	5,05
Vb	endo-OCOCH$_3$	7,07 ... 7,22	1,90	(5,53)	2,80	3,63	3,43 (3,15)	−14,19	(6,17)	(9,53)
IVa	exo-OH	7,10 ... 7,22	—	3,73	3,30	3,45	3,73 (3,22)	−14,47	5,23	5,43
IVc	endo-OH	7,10 ... 7,23	—	(4,46)	2,72	3,68	3,36 (3,15)	−14,22	(6,05)	(9,78)

(m, 4H, arom.), 4.81 (d, 1H, H_{2a}, J $H_{2a,2e}$ = 14.5 Hz); 4.10 (br.s, 1H, H_{3e}), 3.40 (dd, 1H, H_{4a}, J $H_{4a,4e}$ = 13.0, J $H_{4a,3e}$ = 7.0 Hz); 3.23 (dd, 1H, H_{2e}, J $H_{2e,3e}$ = 3.0 Hz); 3.12 (dd, 1H, H_{4e}, J $H_{4e,3e}$ = 4.0 Hz); 2.025 ppm (s, 3H, $COCH_3$).

1-Acetyl-5-(2-hydroxyethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-3-ol (III). Ethylene oxide (0.8 ml, 16 mmoles) was added with cooling in an ice bath to a solution of II (1.0 g, 4.8 mmoles) in glacial AcOH (10 ml). After 3 h the reaction mixture was evaporated, neutralized with aqueous Na_2CO_3, and extracted with $CHCl_3$ (3 × 10 ml). The combined chloroform extracts were dried over $MgSO_4$, filtered, and evaporated to give 1.52 g (130%) of oil which darkened on storage. R_f 0.36 (A), retention time 7.1 min (C). IR spectrum (thin layer): 1060 (C—N); 1320 (C—O stretch); 1500, 1600 (arom. C=C); 1640 (C=O); 2880, 2930 (CH_2); 3100-3500 cm^{-1} (O—H). Mass spectrum: 250 (50) $[M]^+$, 220 (20), 219 (100) $[M - CH_2OH]^+$, 177 (70), 163 (20); 146 (22), 133 (28), 119 (20). PMR spectrum (in $CHCl_3$): 7.30-6.97 (m, 4H, arom.), 4.35 (d, 1H, H_{2a}, J $H_{2a,2e}$ = 14.0 Hz); 4.02 (br.s, 1H, H_{3e}); 3.74-2.63 (m, 7H, CH_2); 1.75 ppm (s, 3H, $COCH_3$).

Benzo[f]-1,5-diazabicyclo[3.2.2]nonen-3-ol (IV). A solution of III (5.1 g) in concentrated hydrobromic acid was refluxed for 6 h, the reaction mixture evaporated, neutralized with aqueous Na_2CO_3, and extracted with chloroform. The combined extracts were dried over $MgSO_4$, filtered, and evaporated. The dark oily residue was distilled in vacuo and crystallized from benzene—hexane 1:3 to give colorless crystals (0.85 g, 22%) with mp 80-100°C. R_f 0.10 (A), 0.60 (B), retention times 5.45 and 5.75 min (C). IR spectrum (KBr): 770 (arom. C—H); 1065 (C—N); 1310 (C—N stretch); 1465 (CH_2 bend); 1485 (arom. C=C); 2870, 2885, 2925, 2970 (CH_2 stretch); 3090 (C—H stretch); 3420 cm^{-1} (O—H). UV spectrum (in ethanol): 207 (4.05), 230 (3.60), 270 (3.21). Mass spectrum: 190 (50) $[M]^+$, 146 (100) $[M - CH_2CHOH]^+$, 145 (50), 131 (20), 119 (25), 118 (45). M 190.1105.

Benzo[f]-1,5-diazabicyclo[3.2.2]nonen-3-ol-1-methiodide (VI). Methyl iodide (2 ml, 32 mmoles) was added to a solution of IV (0.3 g, 1.6 mmoles) in ether (30 ml) and left for 12 h. The precipitate was filtered off and recrystallized from ethanol (2 ml) to give 0.46 g (87%) of colorless crystals with mp 167-170°C (decomp.) and R_f 0.8 (B). IR spectrum 775 (arom. C—H); 1060 (C—N); 1475 (CH_2 bending); 1490 (arom. C=C); 2940 (CH_2 stretch; 3260-3400 cm^{-1} (O—H). UV spectrum (in ethanol): 207 (4.12), 222 nm (4.22). PMR spectrum (in DMF-d_7): 7.6-7.3 (4H, m, arom.); 5.5 (1H, m, H_3); 4.9-4.5 (4H, m, N^+CH_2); 4.4-3.5 (4H, m, CH_2); 3.89 ppm (3H, s, CH_3).

Benzo[f]-1,5-diazabicyclo[3.2.2]nonen-3-acetate (V). Portions of acetic anhydride (0.2 ml, 2 mmoles) and diisopropylethylamine (0.4 ml, 2 mmoles) were added to a refluxing solution of IV (0.2 g, 1.1 mmoles) in benzene (8 ml) until TLC showed the disappearance of starting material (about 8 h reflux, 0.8 ml acetic anhydride + 1.6 ml diisopropylethylamine). The reaction mixture was evaporated, neutralized with Na_2CO_3 solution, and extracted with $CHCl_3$ (4 × 20 ml). After drying with $MgSO_4$ the extract was filtered and evaporated to give a yellow oil. Crystallization from hexane gave 0.2 g (80%) of colorless crystals with R_f 0.45 (A). Slow crystallization gave two types of crystals as needles and prisms.

Benzo[f]-1,5-diazabicyclo[3.2.2]nonene-3-exo-acetate (Va). Mp 139-140°C, needles. IR spectrum (KBr): 750 (arom. C—H); 1030 (C—N); 1230 (C—O stretch); 1460 (CH_2 bend); 1485 (arom. C=C); 1725 (C=O); 2880, 2930, 2960 (CH_2 stretch); 3040 cm^{-1} (C—H). UV spectrum (ethanol): 207 (4.0), 234 (3.3), 270 (3.04). Mass spectrum: 232 (48) $[M]^+$, 172 (25), 146 (100) $[M - CH_2CHOCOCH_3]^+$, 145 (38), 131 (21), 119 (16), 118 (30). M 232.1218.

Benzo[f]-1,5-diazabicyclo[3.2.2[nonene-3-endo-acetate (Vb). Mp 93-95°C, prisms. IR spectrum (KBr): 750 (arom. C—H); 1040 (C—N); 1230 (C—O stretch); 1460 (CH_2 bend); 1485 (arom. C=C); 1730 (C=O); 2880, 2925, 2950 (CH_2 stretch); 3040 cm^{-1} (C—H). UV spectrum (ethanol): 207 (4.0), 234 (3.3), 270 (3.04). Mass spectrum: 232 (32) $[M]^+$, 172 (25), 161 (10), 146 (100) $[M - CH_2CHOCOCH_3]^+$, 145 (35), 131 (30), 119 (20), 118 (35). M 232.1224.

Benzo[f]-1,5-diazabicyclo[3.2.2]nonene-3-exo-ol (IVa). A solution of Va (0.02 g, 0.09 mmole) was refluxed in 1 ml of 0.1 M KOH in 50% ethanol for 1 h. The product was evaporated and extracted with $CHCl_3$ (4 × 5 ml). The extracts were evaporated and the residue distilled in vacuo to give 0.014 g (85%) as colorless crystals with mp 75-77°C.

Benzo[f]-1,5-diazabicyclo[3.2.2]nonene-3-endo-ol (IVb) was obtained similarly from Vb with mp 177-179°C (in a sealed ampul).

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