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DIAZABICYCLOALKANES WITH NITROGEN ATOMS IN BRIDGEHEAD POSITIONS.

24.* SYNTHESIS AND REACTIONS OF BENZO[f]-1,5-DIAZABICYCLO[3.2.2]NONEN-3-ONE

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Benzo[f]-1,5-diazabicyclo[3.2.2]nonen-3-one was synthesized by the oxidation of benzo[f]-1,5-diazabicyclo[3.2.2]nonen-3-ol by dimethyl sulfoxide in the presence of N,N'-dicycohexylcarbodiimide and the reactions of this compound with 2,4-dinitrophenylhydrazine, phenylmagnesium bromide, and condensation with 4-nitro-benzaldehyde were carried out. It was shown that on heating with hydrobromic acid, benzo[f]-1,5-diazabicyclo[3.2.2]nonen-3-one undergoes dealkylation with the formation of 1,2,3,4-tetrahydroquinoxaline.

In continuation of the development of a method of synthesis of functional derivatives of benzodiazabicycloalkenes at the alicyclic part of the molecule, from the previously obtained benzo[f]-1,5-diazabicyclo[3.2.2]nonen-3-ol (I) we synthesized benzo[f]-1,5-diazabicyclo[3.2.2]nonen-3-one (II) and carried out a series of reactions characteristic for carbonyl compounds.

Various reagents were used for the oxidation of compound I at room temperature. On treatment with chromic anhydride in sulfuric acid and ammonium persulfate in various media, no oxidation reaction was observed. When

*For Communication 23, see [1].

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TABLE 1. Characteristics of Compounds II-V

Compound	Empirical formula	mp, °C		IR spectrum (in KBr), cm^{-1}	UV spectrum (in ethanol), λ_{max}, nm (log ε)	PMR spectrum (in $CDCl_3$), ppm (J, Hz)	Mass spectrum, m/z (I, %)	Yield, %
II	$C_{11}H_{12}N_2O$	164...166*	0,45 (A)	770 (arom. C—H), 1050 (C—N), 1465 (CH_2), 1486 (C=C), 1695 (C=O), 2880, 2910, 2930, 2970 (CH_2)	210 (3,61), 238 (3,18, sh.), 270 (3,11)	7,20 (4H, s, arom); 3,79 (4H, d, J=18,2, CH_2); 3,54...3,25 (4H, m, CH_2CH_2)	188 (5) [M]+, 160 (70) [M−CH_2CH_2]+, 132 (45), 131 (100)	75
III	$C_{17}H_{16}N_6O_4$	188...190	0,70 (A)	1320 (C—N), 1345 (NO_2), 1500 (C=C), 1530 (NO_2), 1595 (C=C), 1615 (C=N), 2885, 2950, (CH_2), 3080 (arom.CH), 3320 (N—H)	208 (4,28), 225 (4,21, sh), 262 (4,10 sh), 365 (4,33)	8,98 (1H, d, $H_{3'}$, $J_{H_3'H_5'}$=2,5); 8,18 (1H, d d, $H_{5'}$, $J_{H_5'H_3'}$=2,5; $J_{H_5'H_6'}$=9,5); 7,73 (1H, d, $H_{6'}$, $J_{H_5'H_6'}$=9,5); 7,24...7,10 (4H, m, arom.); 4,18 (4H, d, J=19, CH_2); 3,34 (4H, d, CH_2CH_2)	368 (30) [M]+, 168 (100), 145 (20), 131 (40)	80
IVa	$C_{17}H_{18}N_2O$	157...159	0,38 (A)	780 (arom. CH), 1035 (C—N), 1480 (C=C), 2870, 2930, 2960 (CH_2), 3300 (OH)	208 (4,31), 218 (4,18, sh), 270 (3,24)	7,58...7,50, 7,45...7,24 (5H, m, arom); 7,25 (4H, s, arom); 3,65 (4H, s CH_2); 3,65...3,29 (4H, m, CH_2)	266 (50), [M]+, 161 (70), 146 (100), 145 (50), 131 (20), 118 (40)	16
IVb**	$C_{17}H_{18}N_2O$	233...235	0,27 (A)			7,15 (9H, br..s ,arom.); 4,16 (2H, d.d., CH_2CH_2, J_1=14, J_2=5); 3,31 (4H, d, CH_2, J=16); 3,18 (2H, d.d, CH_2CH_2, J_1=14, J_2=5)		19
V	$C_{25}H_{18}N_4O_5$	252...256	0,90 (A)	1345 (NO_2), 1530 (NO_2), 1600 (C=C), 1670 (C=O), 2880, 2840 (CH_2), 3080, 3110 (CH)	205, 225 (sh), 354	8,40 (4H, d J=9, arom.); 8,29 (4H, d, J=9, arom.); 7,26 (2H, s, 2CH), 7,21 (4H, s, arom.); 3,70...3,60 (4H, m, CH_2CH_2)	454 (100) [M]+, 426 (50) [M−CH_2CH_2]+, 425 (40), 305 (40), 304 (45), 290 (40)	76

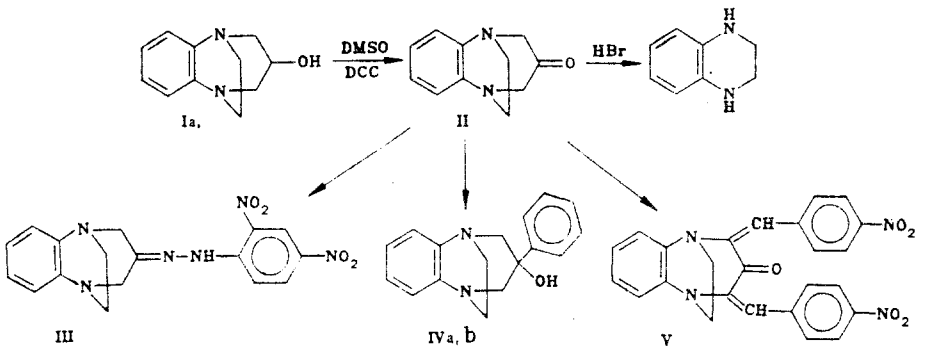
*In a sealed capillary.

**The IR, UV, and mass spectra are similar to spectra of compound IVa.

a complex of chromic anhydride with pyridine is used, the reaction proceeds with a low yield. The presence in the oxidizing agent of reactive groups, as in chloranil and 2,3-dichloro-4,5-dicyanobenzoquinone, leads to the formation of by-products. The best result was obtained with oxidation by the Pfitzner and Moffat method [2] by DMSO at room temperature in the presence of N,N′-dicyclohexylcarbodiimide. In this case, ketone II was isolated in a yield of 75%, which indicates the absence of noticeable stereospecificity of oxidation of the exo- and endo-isomers of compound I, which are present, as has already been shown [1], in an approximately 1:1 ratio in the sample being oxidized. Together with the mass spectrometry and elemental analysis data, the structure of ketone II is confirmed by the appearance in the IR spectrum of an intense band of the carbonyl group at 1695 cm^{-1}, and also by the simplification of the PMR spectrum of ketone II, compared with the spectrum of the 3-hydroxy derivative I [1]. Thus, the signals of the aromatic ring protons of compound II appear in the form of a singlet at 7.20 ppm. The exo- and endo-protons of the CH_2CO groups — in the form of two doublets with SSCC 18 Hz at 3.95 and 3.63 ppm, and the protons of the ethylene bridge — in the form of a symmetric multiplet at 3.54-3.25 ppm.

Compound II undergoes reactions characteristic of ketones. Thus, on treatment with 2,4-dinitrophenylhydrazine in the presence of catalytic amounts of an acid, the corresponding hydrazone III separates out. The presence of a large amount of acid hinders the isolation of the hydrazone, which is readily soluble in acids, and its separation from the unreacted ketone.

In the reaction of compound II with phenylmagnesium bromide besides the unreacted starting compound, a mixture of isomeric derivatives IVa, b is formed. The separation of stereoisomers IVa, b and also the separation from the unreacted compound II were carried out chromatographically. Compounds IVa, b have practically the same IR UV, and mass spectra, but differ in the PMR spectra and melting points. The PMR spectrum of the low-melting isomer IVa (mp 157-159°C) is similar to the spectrum of the low-melting exo derivative Ia [1], while the PMR spectrum of the high-melting isomer IVb (mp 233-235°C) is similar to the spectrum of the high-melting endo-derivative Ib, which may indicate an in-pair similarity of structures of compounds IVa and Ia, IVb and Ib. Thus, the configuration of an exo-hydroxy-endo-phenyl can be ascribed to compound IVa, and the endo-hydroxy-exo-phenyl to compound IVb. In the course of the synthesis, isomers IVa and IVb are formed in comparable amounts, which indicates an equal probability of attack by phenylmagnesium bromide on the carbonyl group, both from the side of the ethylene bridge and from the side of the benzene ring.



Ketone II, having mobile α-protons, readily condenses with aldehydes by the action of alkali. Thus, with p-nitrobenzaldehyde, a dibenzylidene derivative V is formed. Thereby, even in the case of deficiency of p-nitrobenzaldehyde, a dibenzylidene derivative rather than a mono-derivative is formed. This is probably due to the increase in the CH-acidity of the methylene group remaining after the formation of the monobenzylidene derivative. The structure of compound V was confirmed by the IR, UV, PMR, and mass spectroscopy data and elemental analysis data. The relatively low (~20%) intensity of the absorption band of the carbonyl group vibrations agrees with the data in [3] for analogous compounds.

On boiling with hydrobromic acid (under usual conditions of the formation of bicyclic systems [4]) compound II becomes rapidly dealkylated with the formation of 1,2,3,4-tetrahydroquinoxaline. A similar dealkylation is observed for benzo[b]-1,4-diazabicyclo-[2.2.2]octene, but under somewhat more rigorous conditions (prolonged heating at 140°C in hydrobromic acid) [4]. This instability is possibly due to the increased sensitivity of the α-methylene groups of ketone II to nucleophiles, which prohibits the use of hydrobromic acid for the synthesis of compound II.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrophotometer, the UV spectra on a Specord UV-VIS spectrophotometer, and PMR spectra on a Bruker HX-90 spectrometer. The mass spectra were obtained on a

Finnigan MAT-8200 mass spectrometer. The analysis of the reaction mixtures was carried out by TLC on Silufol UV-254 plates in systems: chloroform—ethanol, 10:1 (system A), and also by microcolumn reversed-phase liquid chromatography on a Nucleosil C-18 sorbent with particle size of 5 μm. The diameter of the microcolumn was 2 mm, height 50 mm. Eluent: 1.2 ml of a linear gradient from 30 to 50% MeOH in 0.01 M Na_2HPO_4 (system B). The feeding rate of the eluent was 0.1 ml/min. The eluate was continuously analyzed in UV light at wavelengths of 210 and 250 nm, using a Milichrom chromatograph. Before deposition on the columns the samples were neutralized to pH 7 by a solution of diisopropylamine—water—methanol (1.5:2.5:5.5). The preparative chromatography was carried out on AC-Alufolien Kieselgel 60 F_{254} plates (20 × 20 cm) in system A. The compounds were detected in UV light, strips with the corresponding R_f were cut off, and the fractions were eluted by a chloroform—methanol (5:1) mixture.

The characteristics of the synthesized compounds are given in Table 1. The data of the elemental analysis correspond to the calculated values.

Benzo[f]-1,5-diazabicyclo[3.2.2]nonen-3-one (II). A 0.3 ml portion (4 mmoles) of dry DMSO, 0.1 ml (1.2 mmoles) of pyridine, 0.06 ml (0.8 mmole) of trifluoroacetic acid, and 0.7 g (3.4 mmoles) of N,N'-dicyclohexylcarbodiimide were added to 0.2 g (1 mmole) of compound I [1] in 3 ml of dry benzene, the mixture was stirred and held for 3 days at room temperature. The precipitate was filtered off, washed with benzene (3 × 5 ml). The combined solutions were evaporated, the residue was neutralized with a saturated solution of Na_2CO_3 to pH 8, and extracted with $CHCl_3$ (5 × 10 ml). The chloroform extracts were dried over $MgSO_4$, filtered, and evaporated. The residue was crystallized from hexane, the crystals were sublimed in vacuo (bath temperature not higher than 120°C at 1-2 mm Hg), and crystallized from hexane again. Yield 0.15 g of colorless crystals.

2,4-Dinitrophenyl Hydrazone of Benzo[f]-1,5-diazabicyclo]3.2.2]nonen-3-one (III). A 0.12 g portion (0.60 mmole) of 2,4-dinitrophenylhydrazine and 2 drops of concentrated HCl were added to 0.1 g (0.53 mmole) of ketone II in 20 ml of ethanol. The mixture was boiled for 2 h, cooled, and the precipitate that separated out was recrystallized from acetone. Yield 0.15 g of yellow crystals.

Benzo[f]-1,5-diazabicyclo[3.2.2]nonen-3-phenyl-3-ol (IV). A 2-ml portion of a 2 mmole/liter solution of phenylmagnesium bromide in ether was added to 0.09 g (0.48 mmole) of compound II in 3 ml of absolute ether, the mixture was stirred and held in an inert atmosphere for 24 h at 20°C. The reaction mixture was poured onto ice, extracted with 5 × 10 ml of $CHCl_3$, dried over $MgSO_4$, filtered, and evaporated. The residue was partitioned by twice-repeated chromatography in system A. From a strip with R_f 0.45, 0.036 g (40%) of the starting compound II was isolated. The isomers of IV were extracted from strips with R_f 0.38 and 0.27.

2,4-Bis(4'-nitrobenzylidene)benzo[f]-1,5-diazabicyclo[3.2.2]nonan-3-one (V). A 0.005 g portion of NaOH and 0.08 g (0.54 mmole) of p-nitrobenzaldehyde were added to 0.05 g (0.27 mmole) of compound II in 1.5 ml of absolute ethanol, and the heterogeneous mixture was boiled for 2 h. Then 5 ml of benzene was added, and boiling was continued for another 3 h with gradual addition of benzene to the complete dissolution of the precipitate. The mixture was cooled, the yellow crystals that separated out were filtered off and dried. Yield 0.065 g of compound V.

Behavior of Compound II in Hydrobromic Acid. A 0.03 g portion of compound II was boiled in 1 ml of concentrated HBr in an inert atmosphere, with periodic withdrawal of samples and analyzing them in system B. A rapid decrease in the intense peak with retention time of 6.5 min (compound II) and increase in the peak with the retention time of 4.0 min were observed. After 2 h, when compound II had disappeared completely, the reaction mixture was evaporated, neutralized to pH 8 with Na_2CO_3, and extracted with $CHCl_3$. The chloroform extracts were dried over $MgSO_4$, filtered, and evaporated. The residue was sublimed and crystallized from hexane. Yield 0.013 g (61%) of yellow crystals. The characteristics of the compound obtained corresponded to those of 1,2,3,4-tetrahydroquinoxaline.

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