SYNTHESIS OF 1-HYDROXY-2-(N-SUBSTITUTED) AZATWISTANES

P. P. Kadzyauskas, Yu. A. Malinauskene,
É. P. Butkus, and N. S. Zefirov

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The reductive amination of bicyclo[3.3.1]nonane-2,6-dione with benzylamine or isopropylamine in the presence of sodium borohydride proceeds with the formation of 1-hydroxy-2-(N-substituted)azatwistanes. When 1-hydroxy-2-benzyl-2-azatwistane is refluxed with acetic anhydride, the ring is opened to give 2-acetoxy-6-acetylbenzylaminobicyclo[3.3.1]nonane. The structures of the synthesized compounds were proved by means of the IR and PMR spectra and the results of elementary analysis.

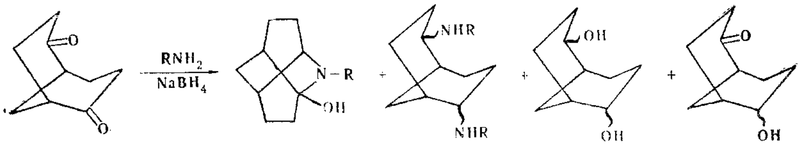
The synthesis of heterotwistanes is an interesting problem – it is appropriate here to cite the adamantane–heteroadamantane analogy, which has been well developed in the literature [1]. Nevertheless, the study that has been devoted to their synthesis is clearly inadquate.

One of the strategies in the synthesis of these compounds consists in the cyclization of 2,6-difunctional derivatives of bicyclo[3.3.1]nonane. Despite the simplicity and attractiveness of this scheme, it has been realized only for the synthesis of oxatwistanes [2].

In the present paper we describe the synthesis of 2-anatwistanes by the reductive cyclization of diketone I with sodium borohydride in the presence of suitable amines. This scheme has been used successfully for the synthesis of 1-substituted 2-azaadamantanes from the corresponding 3,7-disubstituted bicyclo[3.3.1]nonanes [1] and for the synthesis of a number of carcass γ-diketones [3, 4].

1-Hydroxy-2-benzyl-2-azatwistane (II, 56%), 2,6-dibenzylaminobicyclo[3.3.1]nonane (III, 18%, in the form of dihydrochloride VI), and a mixture of a diol and a ketol (IV + V, 25%) are formed when diketone I is refluxed with benzylamine in ethanol in the presence of sodium borohydride and are separated by fractional crystallization and chromatography with a column filled with aluminum oxide.

The formation of 1-hydroxy-2-isopropyl-2-azatwistane (VII) takes place in the analogous reaction of diketone I with isopropylamine in the presence of sodium borohydride; however, it is obtained in only 16% yield, evidently because of the lower stability of the intermediate ketimine formed from diketone I and isopropylamine.



I   II, VII   III, VI   IV   V

II, III R = CH$_2$C$_6$H$_5$; VI R = CH$_2$C$_6$H$_5$·2 HCl; VII R = CH(CH$_3$)$_2$

A broad band with an absorption maximum at ~3400 cm^{-1}, which is characteristic for an associated hydroxy group, is observed in the IR spectrum of azatwistane II. In the case of a dilute solution in carbon tetrachloride the absorption band of the unassociated hydroxy group in II corresponds to 3638 cm^{-1}. This form of azatwistanes II and VII evidently corresponds to the cyclic tautomer, which may exist in equilibrium with the open amino ketone form VIII. However, the IR spectra of these compounds do not contain absorption bands of the carbonyl group of the tautomeric VIII form.

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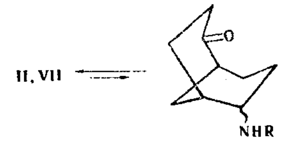
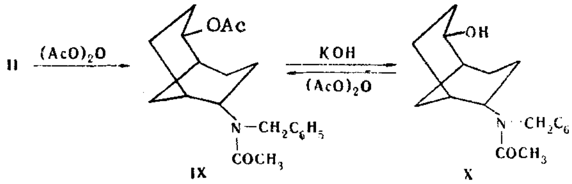


VIII

The PMR spectrum of II contains singlets at δ 7.12 (aromatic protons) and 3.62 ppm (2-CH_2) and multiplets at 2.56 (1-H) and 1.25-2.0 ppm (12 skeletal protons and a hydroxy proton; a shift of the latter to weak field is observed as the temperature is raised).

When azatwistane II is refluxed with acetic anhydride, the ring undergoes opening to give 2-acetoxy-6-acetylbenzylaminobicyclo[3.3.1]nonane (IX) (in quantitative yield), the solvolysis of which leads to 6-acetylbenzylaminobicyclo[3.3.1]nonan-2-ol (X).



Let us emphasize that instances of this sort of opening of cyclic aza derivatives under the influence of acetic anhydride have been described [5].

It is not possible to determine the configuration of the substituents in the 2 and 6 positions with certainty on the basis of the PMR spectra; however, on the basis of general stereochemical considerations, let us specify that opening of azatwistane II should lead to the diendo derivative of bicyclo[3.3.1]nonane.

The method that we have found for the synthesis of azatwistanes is a new method for the preparation of N-substituted derivatives of 1-hydroxy-2-azatwistanes.

EXPERIMENTAL

The IR spectra of the compounds were recorded with a UR-20 spectrometer. The PMR spectra were recorded with a Tesla B-487C spectrometer with hexamethyldisiloxane as the internal standard. Thin-layer and column chromatography were carried out on activity II aluminum oxide.

1-Hydroxy-2-benzyl-2-azatwistane (II). A 4.3-ml (39-mmole) sample of benzylamine was added with stirring to a solution of 6 g (39 mmole) of diketone I [6] in 100 ml of absolute ethanol, and the mixture was heated on a water bath for 2 h. The flask contents were cooled to 20°C, and 3.5 g (92 mmole) of sodium borohydride was added with stirring in small portions at such a rate that the temperature did not rise above 20°C. Stirring was continued for another 3 h, after which the mixture was allowed to stand overnight. The bulk of the solvent was removed by distillation, and the residual sodium borohydride was decomposed in the usual way. The aqueous solution was extracted with ether, and the extract was washed with a small amount of water and dried with $MgSO_4$. The solvent was removed by distillation to give 6.2 g of a mixture of substances [R_f 0.24, 0.26, 0.41, and 0.54; elution with chloroform–methanol (29 : 1)]. Fractional crystallization from a mixture of ether and hexane gave 3.5 g of hydroxyazabenzyltwistane II with mp 84-85°C (from ether–hexane). IR spectrum (CCl_4): 3638 cm^{-1} (OH); the absorption band of a C=O group was absent. PMR spectrum (CCl_4): 7.12 (s, 5H), 3.62 (s, 2H), 2.56 (m, 1H), and 1.25-2.0 ppm (m, 13H). Found: C 79.3; H 9.0; N 5.7%. $C_{16}H_{21}NO$. Calculated: C 79.0; H 8.7; N 5.8%.

The mother liquors from the crystallization were concentrated, the solvent was removed by distillation, and the residue (2.5 g) was chromatographed with a column [elution with chloroform–methanol (29 : 1)]. Fractions with R_f 0.54, 0.41, 0.26, and 0.24 were collected. The fraction with R_f 0.41 was concentrated, and the oily substance was dissolved in absolute ether. The ether solution was saturated with dry hydrogen chloride and worked up to give 1.4 g of dihydrochloride VI with mp 274°C (from absolute ether–methanol). PMR spectrum (d_6-DMSO): 9.62 (m, 4H), 7.3-7.75 (m, 10H), 4.07 (m, 4H), and 1.45-2.3 ppm (m, 12H). Found: C 67.6; H 7.7; N 6.8%. $C_{23}H_{30}N_2 \cdot 2HCl$. Calculated: C 67.8; H 7.9; N 6.9%.

1-Hydroxy-2-isopropyl-2-azatwistane (VII). A 6-g (39-mmole) sample of diketone I was dissolved in 60 ml of isopropylamine, and 3.5 g (92 mmole) of sodium borohydride was added in small portions with stirring, during which the temperature was not allowed to rise above 20°C. The reaction mixture was heated on a water bath for 2 h and allowed to stand overnight. The excess isopropylamine was removed by distillation, and the sodium borohydride was decomposed in the usual way. The aqueous solution was extracted with ether, and the extract was washed with a small amount of water and dried. The ether was removed and the residue (5.6 g) was dissolved in absolute ether. The ether solution was saturated with dry hydrogen chloride, and the precipitate was removed by filtration to give 1.1 g of the hydrochloride of VII with mp 183-185°C. Found: C 61.9; H 9.9; N 5.8%. $C_{12}H_{21}NO \cdot HCl$. Calculated: C 62.2; H 9.6; N 6.0%. The ether solution was concentrated to give 4.5 g of a mixture of the diol and ketol (IV + V).

A 0.2-g sample of the hydrochloride of VII was dissolved in 4 ml of water, 0.2 g of potassium carbonate was added, and the mixture was stirred for 30 min. The aqueous solution was extracted with ether, and the extract was washed with water and dried. The solvent was removed from the extract to give 0.17 g of hydroxyisopropylazatwistane VII with mp 115°C (from ether—hexane). IR spectrum (CCl_4): 3638 cm^{-1} (OH). PMR spectrum ($CDCl_3$): 3.73 (m, 1H), 2.8 (m, 1H), 1.33 (OH, s, 1H), 1.2-1.93 (m, 12H), and 0.95 ppm (d, 6H). Found: C 73.5; H 10.7; N 7.2%. $C_{12}H_{21}NO$. Calculated: C 73.8; H 10.8; N 7.2%.

2-Acetoxy-6-acetylbenzylaminobicyclo[3.3.1]nonane (IX). A) A mixture of 0.97 g (3.9 mmole) of hydroxybenzylazatwistane II, 0.5 g of anhydrous sodium acetate, and 5 ml (53 mmole) of acetic anhydride was heated at 100°C for 1 h, after which it was cooled and filtered, and the filtrate was evaporated to dryness in vacuo to give 1.32 g of diacetyl derivative IX with mp 82-83°C (from ether-acetone). IR spectrum (mineral oil): 1742 (ester C=O) and 1668 cm^{-1} (amide C=O). PMR spectrum (CCl_4): 7.12 (m, 5H), 4.45-4.80 (m, 3H), 1.25-2.05 (m, 13H), and 1.83 ppm (CH_3, s, 6H). Found: C 73.2; H 8.2; N 4.3%. $C_{20}H_{27}NO_3$. Calculated: C 72.9; H 8.3; N4.2%.

B) A 0.1-g (3.4-mmole) sample of X was dissolved in 1 ml (10.6 mmole) of acetic anhydride, 0.05 g of anhydrous sodium acetate was added, and the mixture was heated at 100°C for 1 h. It was then cooled and filtered, and the filtrate was evaporated to dryness to give 0.13 g of diacetyl derivative IX with mp 82-83°C. The IR spectrum of the product was identical to the spectrum of an analytical sample of IX.

6-Acetylbenzylaminobicyclo[3.3.1]nonan-2-ol (X). A 2.3-g (40-mmole) sample of potassium hydroxide was dissolved in 10 ml of methanol, 0.67 g (2 mmole) of diacetyl derivative IX was added, and the mixture was refluxed for 1 h and allowed to stand overnight. The methanol was removed by distillation, and the residue was dissolved in a small amount of water. The aqueous solution was extracted with ether, and the ether layer was washed with a small amount of water and dried. The solvent was removed by distillation to give 0.45 g N-acetate X with mp 131-132°C (from ether—hexane). IR spectrum (mineral oil): 3425 (OH) and 1640 cm^{-1} (C=O). PMR spectrum (CCl_4): 7.12 (m, 5H), 4.5 (m, 2H), 3.7 (H—COH, m, 1H), 2.58 (OH, s, 1H), 1.1-2.25 (m, 13H), and 1.9 ppm (CH_3, s, 3H). Found: C 74.8; H 8.7; N 4.9%. $C_{18}H_{26}NO_2$. Calculated: C 75.2; H 8.8; N 4.9%.

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