ORGANOBORON METHOD FOR THE SYNTHESIS OF 8-AZAGONANES

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A method was developed for obtaining the heteroanalogs of steroidal 8-azagonanes using intermediate organoboron compounds with a boron—oxygen bond or esters of boric acid. 8-Azagona-1,3,5(10)-triene, D-homo-8-azagona-1,3,5(10)-triene, and D-dihomo-8-azagona-1,3,5(10)-triene were synthesized.

Methods for the synthesis of 8-azagonanes are being developed [1]. The method that we have developed for the synthesis of 8-azagonanes using organic reagents with a B—O bond is based on the heterolytic cleavage of the C—O chemical bond and not the B—O bond as the stronger bond under thermolysis conditions, which ultimately leads to cyclization and the formation of a new C—C bond on reaction with a nucleophilic reagent. Organic compounds with a hydroxyethylamino function in which the hydroxy group undergoes boron esterification and the resulting boron ester of the starting substance undergoes thermal decomposition serve as starting compounds for this purpose.

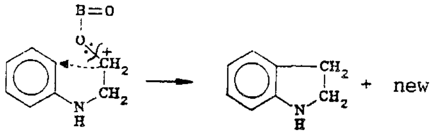
$$(1)\ \mathrm{Ar{-}NH{-}CH_2{-}CH_2{-}OH} + \mathrm{H_3BO_3} \rightleftarrows \mathrm{Ar{-}NH{-}CH_2{-}CH_2OBO} + 2\mathrm{H_2O}$$

$$(2)\ \mathrm{Ar{-}NH{-}CH_2{-}CH_2} \not{\vdots}\ \mathrm{O{-}B{=}O} \xrightarrow{\Delta} \mathrm{Ar{-}NH{-}CH_2{-}\overset{+}{C}H_2} + \mathrm{O{=}\bar{B}{=}O}$$

$$(3)\ \mathrm{Ar{-}NH{-}CH_2{-}\overset{+}{C}H_2} \longrightarrow \mathrm{Ar{-}NH{-}CH_2{-}CH_2} + \mathrm{H^+}$$

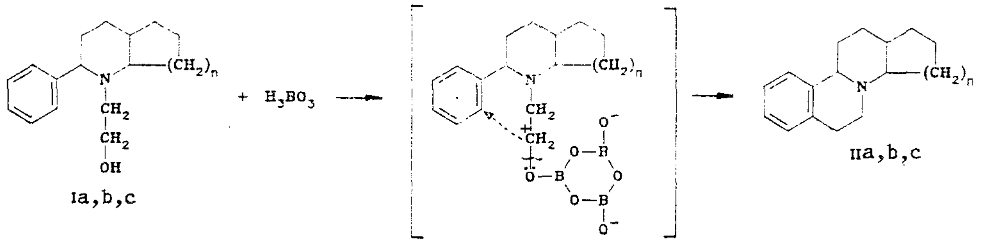
$$(4)\ \mathrm{H^+} + \mathrm{O{=}\bar{B}{=}O} \longrightarrow \text{new}$$

This cyclization with the inclusion of a nitrogen atom in the heteroring proceeds via a mechanism of the intramolecular electrophilic substitution type. Previously one of us has found [2] that the boron ester of N-(2-hydroxyethyl)phenylamine cannot be distilled even at reduced pressure but decomposes on heating with the formation of 2,3-dihydroindole.



In the present research we used a similar type of cyclization in order to synthesize 8-azagonanes. The starting 1,5-diketones were treated with monoethanolamine under reductive alkylation conditions [3, p. 483]. As a result, we obtained N-(2'-hydroxyethyl)-2-phenyl[5,6-a]cyclopento(hexo, hepto) derivatives (Ia-c) of piperidine, which were subjected to boron esterification and thermolysis with a boiling solvent to give the desired products IIa-c.

8-Azagona-1,3,5(10)-triene (IIa), D-homo-8-azagona-1,3,5(10)-thiene (IIb), and D-dihomo-8-azagona-1,3,5(10)-triene (IIc) were synthesized in this way.



Ia,b,c

IIa,b,c

I, II a n=1; b n=2; c n=3

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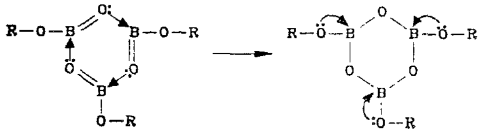
The dehydration of the alcohols in the presence of equimolar amounts of orthoboric acid proceeds with the formation of intermediate esters of metaboric acid [4], which are unknown in individual form and readily undergo cyclization to the corresponding boroxoles or trimers of metaboric acid.



The C—O chemical bond in boroxoles should be polarized significantly due to shifting of the unpaired electrons of the oxygen atom to the free orbital of the boron atom, which promotes its heterolysis under pyrolysis conditions [5]. In this connection in our syntheses of 8-azasteroids I and H_3BO_3 were taken in a ratio of 1:1, as for RO—B=O, which increases the yields of desired products IIa-c as compared with the yields for a stoichiometric ratio of reagents I and H_3BO_3 of 3:1 as for $(RO)_3B$.

EXPERIMENTAL

The electron-impact mass spectra were recorded with a Varian CH-7A spectrometer with direct introduction of the substances into the ionization source; the accelerating voltage was 3.9 kV, the ionizing voltage was 70 eV, the temperature of the ionization chamber was 200°C, the range of the investigated masses was 30-1000, and the discharge was 2-3 thousand.

The IR spectra of IIa-c (thin layers) were recorded with a UR-20 spectrometer: ν_{max} 1500, 1600, 3040 (arom.); 2800, 2900 cm^{-1} (aliph.).

The results of elementary analysis of Ia-c and IIa-c were in agreement with the calculated values.

8-Azagona-1,3,5(10)-triene (IIa, $G_{16}H_{21}N$). A mixture of 2.2 g (0.01 mmole) of 1-phenyl-3-(2-oxocyclopentyl)-1-propanone and 0.6 g (0.01 mmole) of monoethanolamine in 150 ml of water was refluxed for 4 h, after which it was cooled and treated with 0.2 g of $NaBH_4$, and the mixture was allowed to stand for 10 h. Dilute hydrochloric acid was added carefully dropwise to the solution until hydrogen evolution ceased, after which the solution was evaporated to dryness on a water bath in the vacuum created by a water aspirator, and the resulting oil [2.5 g (∿90%)] was extracted with 50 ml of ethyl acetate. Removal of the solvent by distillation gave 2.6 g (94%) of Ia ($C_{16}H_{23}NO$). The colorless oil had M^+ 245 (I_{rel} 25%).

A 60-mg (0.01 mmole) sample of orthoboric acid and 150 ml of xylene were added to 2.5 g (0.01 mmole) of Ia, and the mixture was refluxed with a Dean—Stark adapter until the water had been removed completely. The solvent was removed by distillation to dryness, and the residue was extracted with 50 ml of a mixture of methanol with petroleum ether (1:1). The solvent was removed by distillation, and the residue was crystallized from ethyl acetate—hexane (1:1) to give 1.6 g (65%) of IIa with M^+ 227 (I_{rel} 41%) and M^+ 198 (I 100%). The purity of IIa and the end of the reaction were monitored by TLC on Al_2O_3 in a cyclohexane—ether system (3:1). Substance IIa was identified as the perchlorate $C_{16}H_{21}N \cdot HClO_4$ with mp 229°C.

D-Homo-8-azagona-1,3,5(10)-triene (IIb, $C_{17}H_{23}N$). As in the synthesis of IIa, the reaction of 2.2 g (0.01 mmole) of 1-phenyl-3-(2-oxocyclohexyl)-1-propanone and 0.6 g (0.01 mmole) of monoethanolamine gave Ib, with M^+ 259 (I_{rel} 35%), in 94% yield. $C_{17}H_{25}NO$.

A 60-mg (0.01 mmole) sample of orthoboric acid and 150 ml of xylene were added to 2.5 g (0.01 mmole) of Ib, and the synthesis was carried out as described for IIa to give 1.7 g (67%) of IIb with M^+ 241 (I_{rel} 45%) and mp 236°C. $C_{17}H_{23}N \cdot HClO_4$.

D-Dihomo-8-azagona-1,3,5(10)-triene (IIc, $C_{18}H_{25}N$). As in the synthesis of IIa, the reaction of 2.2 g (0.01 mmole) of 1-phenyl-3-(2-oxocycloheptyl)-1-propanone and 0.6 g (0.01 mmole) of monoethanolamine gave Ic, with M^+ 273 (I_{rel} 37%), in 91% yield. $C_{18}H_{27}NO$.

A 60-mg (0.01 mmole) sample of orthoboric acid and 150 ml of xylene were added to 2.5 g (0.01 mmole) of Ic, and 1.7 g (67%) of IIc, with M^+ 255 (I_{rel} 42%) and mp 241°C, was synthesized as described for IIa. $C_{18}H_{25}N \cdot HClO_4$.

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OXIDATION OF 1-AMINOBENZIMIDAZOLES. SYNTHESIS AND PROPERTIES OF 1,1'-AZOBENZIMIDAZOLES*

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1-Amino-2-R-benzimidazoles are oxidized by lead tetraacetate to give, depending on the substituent in the 2-position, either to 1,1'-azobenzimidazoles (R = H, CH_3, C_6H_5, Cl, $N(CH_3)_2$) or 3-R-benzo-1,2,4-triazines (R = NH_2, $NHCH_3$, NHC_6H_5, OH). The factors affecting the course of the reaction are discussed. The physicochemical properties of the 1,1'-azobenzimidiazoles obtained have been examined.

1,2-Diaminobenzimidazole (Ia) is oxidized by lead tetraacetate [2] or manganese dioxide [3] to give good yields of 3-aminobenzo-1,2,4-triazine (IIa) as the sole product. By analogy with other, similar reactions of N-aminoazoles, this reaction is assumed to involve the intermediate formation of a highly reactive N_1-nitrene, which intramolecularly attacks atom $C_{(2)}$ of the imidazole ring. If this reaction does in fact occur, other 1-aminobenzimidazoles should react similarly, thus providing a route to the highly inaccessible 3-R-benzo-1,2,4-triazines. In order to test this hypothesis, we have examined the oxidation of 1-aminobenzimidazole (Ib) and its 2-substituted derivatives (Ic-h), together with some other compounds.

The oxidation of 1-aminobenzimidazoles with lead tetraacetate is extremely complex, often giving difficultly-separable mixtures and unstable compounds. The products are highly dependent on the substituent present in the 2-position. For example, oxidation of the parent benzimidazole (Ib) with a small excess of lead tetraacetate in dichloromethane at 20°C gives, instead of the expected benzotriazine (II) (R = H), 32% of 1-acetylbenzimidazole (IVa), and 5% of the hitherto unknown 1,1'-azobenzimidazole (IIIb). When this reaction was carried out in the presence of calcium oxide (to bind the acetic acid liberated), in addition to the tetrazine (IIIb) (5%), the second reaction product was benzimidazole (perhaps as a result of hydrolytic cleavage of (IVa) under these conditions [6, p. 38]). Oxidation of 1-amino-5,6-dimethylbenzimidazole with lead tetraacetate gave 10% of 1-acetyl-5,6-dimethylbenzimidazole (IVb) only. The yield of the tetrazene (IIIb) was increased to 25% when the oxidation of (Ib) was carried out with bromine water.† Under similar conditions, 1-amino-5,6-dimethylbenzimidazole was oxidized to the tetrazene (V) (10%) and 5,6-dimethylbenzimidazole (55%).

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*For preliminary communication, see [1].

†Attempts to obtain the tetrazene (IIIb) by oxidation of 1-aminobenzimidazole with mercuric oxide were unsuccessful [7].

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