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The first benzodiazepine *o*-quinodimethane: generation and Diels–Alder reactions

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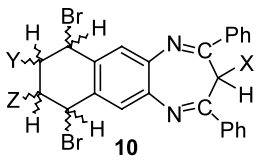
Abstract—7,8-Bis(dibromomethyl)-3-bromo-2,4-diphenyl-3*H*-benzodiazepine **1** was used as a precursor for the benzodiazepine *o*-quinodimethane **2**, which was trapped by in situ reactions with dienophiles.

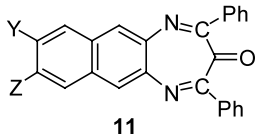
Over the last decade the chemistry of *o*-quinodimethanes (*o*-QDM) has gained increasing interest.[1] The unstable and reactive *o*-QDM are commonly generated in situ from a suitable precursor. Various methods for the generation of these *o*-QDM intermediates have been reported, e.g. electrocyclic ring opening of cyclobutaheterocycles,[2] cheletropic extrusion of SO_2 from sulpholenes[3] and 1,4-elimination of bis(halomethyl) or bis(dihalomethyl) derivatives.[4] Among them the bis(halomethyl) approach is very suitable since these precursors are easily accessible, the reactions proceed at much lower temperatures than the ones required for the cheletropic elimination of SO_2 and the resulting *o*-QDM can be conveniently trapped in situ to afford the adducts in good yield. Moreover, the Diels–Alder reactions of *o*-QDM with dienophiles have proven to be efficient and powerful methods to build polycyclic aromatic compounds.[1]

As the benzodiazepine ring is incorporated in a number of natural products[5] and various compounds of pharmacological interest[6] we embarked on a study aimed at the generation of the benzodiazepine *o*-QDM system **2** (Scheme 1) and its cycloaddition with various dienophiles to produce polycyclic benzodiazepines. Our synthesis utilized the tandem Diels–Alder aromatization reaction, which proceeds through the *o*-QDM intermediate **2** brought about by the action of sodium iodide on the 7,8-bis(dibromomethyl)-3-bromo-2,4-diphenyl-3*H*-benzodiazepine **1** in dry DMF at 55°C for 45 min under argon, whereupon the cycloadducts **3**–**8** were isolated in satisfactory yields. The 3-bromoderivative **1** was used as starting material since the formation of the 3-nonbrominated derivative failed.[7] However, during the reaction the bromine in the 3-position is most probably substituted by iodine giving **2b**. This allylic iodine can be readily reduced in the presence of DMF homolytically yielding the unsubstituted 3-CH_2 group. In addition, in all the reactions studied a small amount (2–3%) of the corresponding keto derivative **11** was also isolated. From the isolation of **11** it can most probably be concluded that, to a small extent the allylic iodine remained unchanged and was replaced during the workup procedure by a hydroxyl which subsequently gave compound **11** by oxidation.

Intermediate dibromo adducts **10** could not be isolated because under the experimental conditions they aromatize with loss of 2HBr. It should also be noticed that from the reaction with *N*-phenylmaleimide a second product **7** was always formed in 20% yield. The formation of **7** can be explained by accepting a substitution of one bromine of **10** by iodine followed by its homolytical reduction and subsequent loss of one molecule of HBr.



10



11

When the reaction was carried out at higher temperatures (80 and 120°C) the Diels–Alder reaction proceeded successfully, but a transformation of the diazepine ring to the quinoxaline derivative **9** was also observed.[8] This remarkable result rules out the possibil-

Keywords: benzodiazepines; *o*-quinodimethanes; Diels–Alder reactions.

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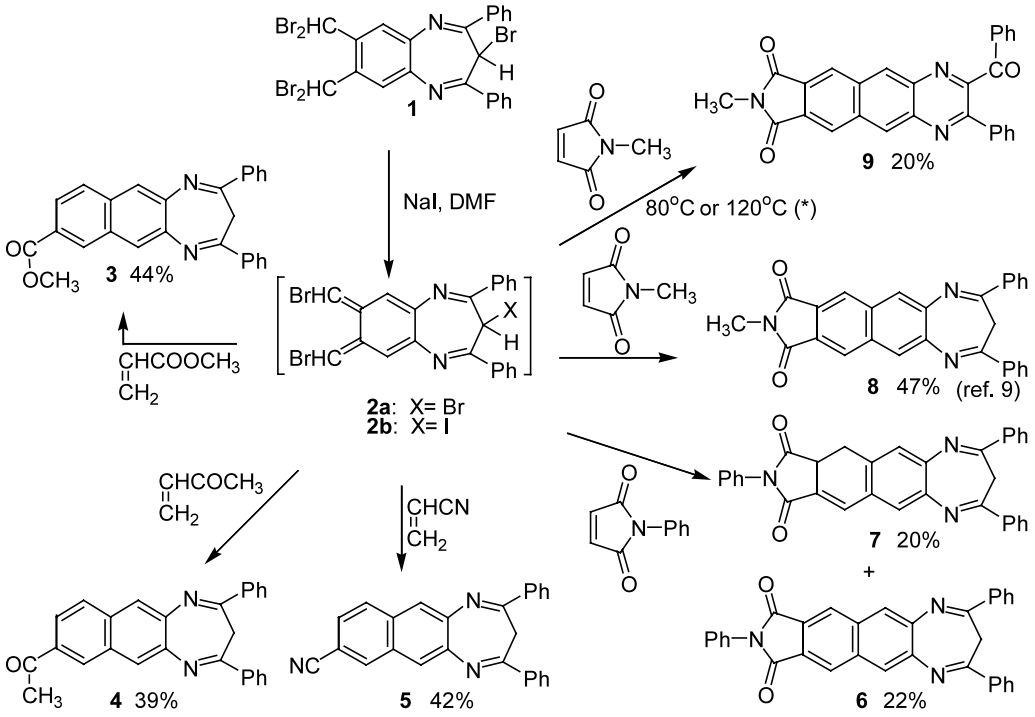

Scheme 1.

ity of formation of benzodiazepine *o*-quinodimethane using sulfolenes as starting materials, where even higher temperatures are required.

In summary, a route leading to the benzodiazepine quinodimethane **2** and its in situ reaction with dienophiles yielding polycyclic aromatic derivatives[9] of possible biological interest[1,5] has been described. To our knowledge this is the first example of the formation of quinodimethane derivatives containing a ring other than five- or six-membered. Further applications of these intermediates in cycloaddition reactions are being studied.

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9. (a) Selected data for compound **8** are given: mp 257–259°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.38 (s, 2H), 8.25 (s, 2H), 8.01–8.05 (m, 4H), 7.26–7.49 (m, 6H), 3.83 (br s,

1H), 3.26 (s, 3H), 1.68 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.17, 160.76, 142.27, 137.14, 132.43, 131.41, 129.25, 128.93, 128.20, 127.60, 124.62, 34.77, 24.29; MS [m/z (%)]: 429 (100) M^+; (b) due to the hindered inversion of the diazepine ring, the methylene protons of the achiral compound **8** are differentiated and give very broad singlets at $\delta = 1.68$ and 3.83. The signal at 1.68 can be assigned to the proton in the *endo* site of the diazepine ring, where it is shielded by both C=N anisotropy cones (+). On the other hand, the *exo* proton being closer to the deshielding cones of the two phenyls and of the two C=N bonds resonates at much lower field. The same discrimination of the methylene protons is observed in all other derivatives **3**–**7**.