Three- and Fourfold Bridgehead-Substituted Tribenzoquinacenes**

By Andreas Schuster and Dietmar Kuck*

Dedicated to Professor Michael Hanack on the occasion of his 60th birthday

The threefold benzo-stabilized triquinacene 1, one of the three prototypic centrotriindanes, provides, in contrast to the parent compound, an opportunity to study reactions at the four bridgehead positions through the formation of stable, well-crystallizing compounds. As we were recently able to show in collaboration with de Meijere et al. [2] the threefold benzoannelation in the case of 1 also contributes considerably to the stabilization of anionic and olefinic derivatives of this system. We now present the particularly stable olefin 3, which is readily accessible from 1 and which affords a variety of novel bridgehead-substituted tribenzoquinacenes in some, in part, unusual reactions.

The tribenzoquinacene 1 is accessible via two routes[2, 3] and, despite its extremely poor solubility, can be converted almost quantitatively into the C3b symmetrically substituted tribromo derivative 2 (Scheme 1). Aminolysis of 2 with di-methylamine affords the tribenzo(dihydro)acenaphtalen 3, also in high yields. In contrast to the analogously prepared dihydroacenaphtalenes, [6] crystalline 3 is absolutely air-stable—a remarkable property in view of the two strongly pyramidalized olefinic atoms C1 and C10.[7, 8] The analogous bis(tri-methylsilyl) compound is likewise accessible from 1, but is far less stable than 3.[12, 9]

Surprisingly, aminolysis of 2 leads to the triamino compound 4 with C3 symmetric substitution. The constitution of this compound, which is also obtainable in good yields, is unequivocally confirmed by its NMR spectrum (Table 1). The 1,4,10-triamine is thus the first triquinacene with hetero-substitution at the central bridgehead to be obtained in a direct synthesis.[10, 11] Attempts to explain the unexpected reaction of 2 with ammonia by further experiments were hitherto not very successful.[12] The intermediary analogue of 3 (H instead of Me, 3’) is, in contrast to 3, apparently not sufficiently kinetically stabilized.[13]

Two of the reactions of 3 carried out with 1,3-dipolar agents deserve special mention, namely those with azides (Scheme 2). 3 reacts smoothly with phenyl azide to give the regioisomer 9, a triquinacene substituted by nitrogen at all four bridgehead atoms. Presumably, steric factors are mainly responsible here for the high regioselectivity. On the other hand, with trimethylsilyl azide we could not isolate the expected cycloaddition products, despite all measures to exclude moisture. Instead the 1-azido-4,7-bis(dimethylamino) derivative 6 was obtained in good yields, once again as a well-crystallizing compound. The NMR data and thermolysis results indicate that the three outer bridgehead atoms carry substituents.

![Scheme 1. Syntheses starting from tribenzoquinacene 1](image-url)

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**[3]** Benzannelated Centropolyquinanes, Part 10. This work was supported by the Deutsche Forschungsgemeinschaft—Part 9: D. Kuck, A. Schuster, R. A. Krause, J. Org. Chem. 56 (1991) 3472–3495.

A number of fourfold heterosubstituted tribenzoquinacenes can be prepared from the olefin 3. Thus, 3 reacts at low temperatures with bromine to give the dibromide 10 (Scheme 2), which can be converted as expected with dimethylamine into the, once again, $C_{3v}$ symmetric 10-bromo-1,4,7-tris(dimethylamino)tribenzoquinacene 11. All attempts at the solvolysis of the C19-Br bond have so far failed.\(^{11}\)

Irradiation of a suspension of 12 in cyclohexane at room temperature (quartz filter) leads to complete deamination to the tetracycle 14. Actually the product is formed in only 16% yield, together with large amounts of polymeric material, but it can be isolated in pure form by medium pressure chromatography (MPLC) and slow crystallization. Surprisingly, it is very soluble compared to many other tribenzoquinacenes.

Table 1. Physical data of selected compounds.\(^{5}\)

<table>
<thead>
<tr>
<th>Compound</th>
<th>$^1$H NMR (CH$_2$Cl$_2$)</th>
<th>$^{13}$C NMR (CH$_2$Cl$_2$)</th>
<th>MS (EI 70 eV)</th>
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<td>3</td>
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<tr>
<td>4</td>
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<td>m/z 409</td>
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<tr>
<td>6</td>
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<td>m/z 409</td>
</tr>
<tr>
<td>7</td>
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</tr>
<tr>
<td>8</td>
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<td>m/z 409</td>
</tr>
<tr>
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<td>m/z 409</td>
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</table>

The photolytic deamination of the cycloadducts 12 and 13 is surprising. In the tribenzotriquinacenes this process is possibly facilitated by radicals generated in the course of the deazotization and is additionally favored by the formation of highly conjugated isodine intermediates. Also consistent with this hypothesis is the ring-opening of 13 to give 17.

The diaminoolefin 3 and the bridgehead-substituted tribenzotriquinacenes presented here for the first time prompt further investigations. Thus, the strictly elliptical orientation of up to four vicinal substituents on the convex side of the molecule with the rigid triquinacene framework could lead to concerted dipolar interactions. The consequences of the particular stereochemistry of such highly functionalized spherical molecules for structure and reactivity should be studied in more detail.

Experimental Procedure for Selected Compounds

2: A suspension of tribenzotriquinacene 1 (560 mg, 2.00 mmol) in tetrachloromethane (100 mL) was treated dropwise at 30 °C with 6.00 mL of a 1.0 M solution of phenyl azide in tetrachloromethane (6.00 mmol). The suspension was additionally irradiated with a photolamp (500 W). After very rapid uptake of the bromine (effervescence!), the solvent was removed and the yellow-brown residue recrystallized from toluene. 2 (790 mg, 94%) was obtained in the form of colorless crystals; m.p. 258 °C (decomp.).

3: A 0.5 mg (1.00 mmol) was frozen in anhydrous benzene (84%) and the mixture stirred for 24 h at room temperature. Methanol was then added and the solution slowly evaporated. 

4: As described for 3, 2 (517 mg, 1.00 mmol) was allowed to react in benzene (precooled to −40 °C) with liquid ammonia (10 mL) in a sealed tube. After workup and recrystallization from CH2Cl2/n-hexane 4 (248 °C (decomp.)).

5: A solution of 3 (364 mg, 1.00 mmol) in dichloromethane (10 mL) was treated with phenyl azide (300 mg, 2.50 mmol) and the mixture stirred for 4 h at room temperature. Methanol was then added and the solution slowly evaporated. 

6: To a solution of 3 (364 mg, 1.00 mmol) in anhydrous dichloromethane precooled to −60 °C was added dropwise a 50.0 mm solution of bromine (1.00 mmol) in dichloromethane (20 mL) over 6 h using a fine-bore dropping funnel. After warming to room temperature, the suspension was evaporated down to a viscous oil to a volume of 10 mL and treated with an equal amount of anhydrous ethyl acetate. The precipitated crystals were recovered by suction and recrystallized from CH2Cl2/MeOH furnished 11 (65 mg; 54%) in the form of colorless crystals; m.p. 251 °C (decomp.).

11: Aminolysis of 10 (151 mg, 250 mmol), analogously to the reaction of 2 with dimethylamine, afforded a crude product, which, after recrystallization from CH2Cl2/MeOH furnished 11 (65 mg; 54%) in the form of colorless crystals; m.p. 278 °C (decomp.).

14, 16, and 17: The cycloadducts 12 (m.p. 272 °C) and 13 (m.p. 330 °C) were obtained from by standard methods.


19. According to force field calculations (MM2 (87)) the pyramidalization angles [?] are 39.3° and 90°.


23. No reaction was observed upon heating 11 with NH3/amine in an autoclave at 100 °C and with KOH/triethylenglycol up to 120 °C.

24. A. Greenberg, D. F. Maiorana, D. F. Ammonium propane oriented to the 1,10 double bond attacks electrophilically at C1.
1,3-Dipolar Cycloaddition as the Key Reaction in the Synthesis of Potent Renin Inhibitors

By Günter Benz,* Rolf Henning, and Johannes-Peter Stasch
Dedicated to Professor Karl Heinz Bichel on the occasion of his 60th birthday

The renin–angiotensin system plays a central role in the pathogenesis of hypertension, mostly via the circulating vasoconstrictor angiotensin II. Although Angiotensin-Converting Enzyme Inhibitors (ACE Inhibitors) like captopril and enalapril have already been introduced to therapy, emphasis has been directed toward renin inhibitors in recent years because of their supposedly better selectivity.

The most important reaction of renin is the proteolysis of the N-terminus of the globular protein angiotensinogen to the decapeptide angiotensin I. If the Leu-Val peptide bond in 1 cleaved in this reaction is replaced by an (9-hydroxyethylene amide bond surrogate, renin inhibitors of the type 2 are obtained. Because these molecules resemble the transition state for cleavage by aspartyl proteases they possess a high affinity for renin but are not cleavable by the enzyme. Many renin inhibitors are rapidly degradated in vivo. This proteolysis should be hampered when the C-terminal amide bond is inverted. For this reason we propose renin inhibitors of the type 3 which has both modifications—the inverted peptide bond and the hydroxyethylene unit. To maintain the topology of the peptide chain the adjacent amino acid must have the D-configuration.

The 1,3-dipolar cycloaddition of allylamines with N-benzyl nitrones provides an easy access to this type of structure in which two stereocenters are generated early in the reaction sequence. The stereochemical course of the reaction can be influenced either by chiral nitrones or by chiral allylamines. The synthesis of the isoxazolidines and a potent renin inhibitor 14 is shown in Scheme 1.

N-Boc-allylamine was prepared in four steps from N-Boc-phenylalanine. The subsequent reaction with benzyl nitrone at 140 °C in mesitylene led after 8 h to a mixture of four diastereomeric isoxazolidines, in the ratio 7a (1R,3S,4S) 0.75, 7b (1S,3S,4S) 1.00, 7c (1S,3R,4S) 0.60, 7d (1R,3S,4S) 0.05.

Scheme 1. a) Mesitylene, 140 °C, 8 h, 52% 7; b) SiO₂, chromatography, n-hexane/ether 7:3; c) NH₂HCO₂H, 10% PhO/C, CH₂OH, reflux, 60 min; d) n-C₆H₄(CO)₂O, NEt₃, CH₂OH; e) 4 N HCl, dioxane, 30 min; f) (S')-cyclopentylglycine 11, dicyclohexylcarbodiimide (DCC), hydroxybenzotriazole (HOBT), diisopropylcarbonyl-Phe 13, DCC, HOBT, DIPEA.