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SYNTHESIS OF NIDO-CARBORATE CONTAINING THIOUREAS

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Summary: The preparation of water-soluble nido-carborate containing cyclic thioureas is described. Their preparations exemplifies the possibilities to introduce boron into molecules for their use in neutron capture therapy.

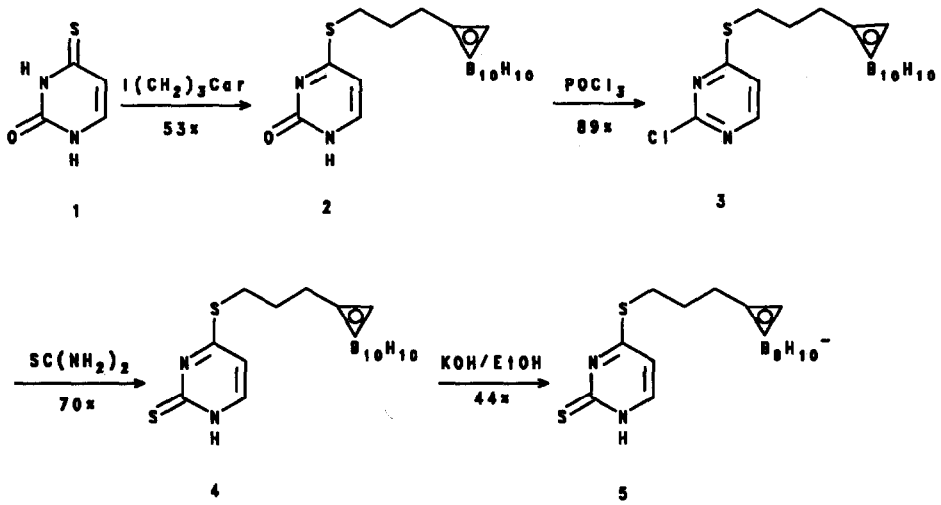
Recently, a greatly renewed interest can be noted in the preparation of boron-containing tumor-seeking molecules for neutron capture therapy.[1] The successful application of this mode of cancer therapy requires the preparation of water-soluble and hydrolytically stable compounds. The carborane clusters, especially 1,2-dicarba-closo-dodecaborane (o-carborane), have been used frequently for this purpose.[2] However, the molecules containing this moiety tend to be water-insoluble. The carborane cage can be degraded with base to the corresponding nido-undecaborate compound, which is water-soluble[3] . The use of alkaline reaction conditions during the synthesis could thus lead to an inadvertent degradation of the cage.

We wish to report here that the carborane cage can be let intact when the alkalinity of reaction steps is carefully controlled. This is illustrated by the preparation of boron-containing cyclic thioureas, which have been proposed as suitable boron carriers for neutron capture therapy of melanomas[4] . Thiouracil derivatives which contain the dihydroxyboryl group have been described recently[5] .

4-(3-o-carboranylpropyl)thio-2-thiouracil[6] **(4)** was prepared from iodopropylcarborane and 4-thiouracil[7] **(1)** (Scheme 1). It was converted to the nido-undecaborate [8] **5** by refluxing with a 2.5 molar excess of KOH in EtOH for 24 h. Degradation of the cage did not occur when iodopropylcarborane was treated with **1** after addition of equimolar amounts of NaOH in the synthesis of **2**.

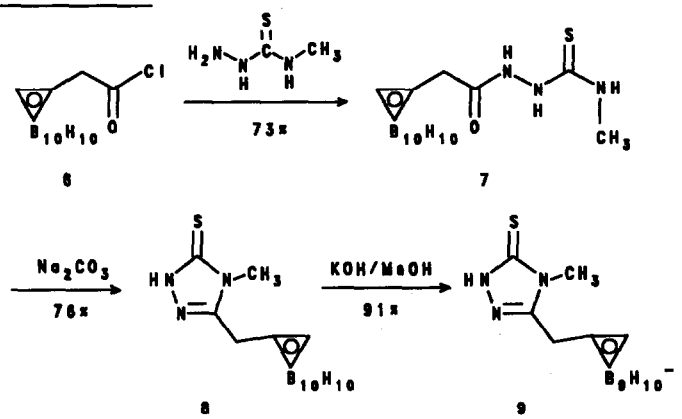
3-[1-(o-carboranylmethyl)]-4-methyl-5-thio-1,2,4-triazol [9] **(8)** could be cyclized with Na_2CO_3 from the corresponding thiosemicarbazide[10] **7** (Scheme 2). By choosing a reaction temperature of 60 °C and one hour reaction time, the degradation of the cage could be avoided. When heating to

Scheme 1:



100 °C, the cage was degraded noticeably already after 10 min. The water-soluble degradation product[11] 9 was obtained after refluxing with KOH/MeOH.

Scheme 2:



The thiosemicarbazide (7) could be prepared without degradation of the cage by slowly adding carboranylacetyl chloride[12] to an excess of 4-methyl-3-thiosemicarbazide at 30 °C. Nitrogen base compounds are otherwise known to degrade the cage very readily.

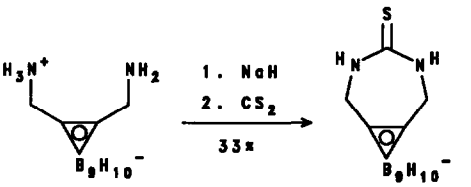
This is demonstrated in the preparation of 1,2-bis-(aminomethyl)-nidocarborate from 1,2-bis-(chloromethyl) carborane, where the degradation of the cage occurs in aqueous ammonia at 60 °C in the course of a few hours. We could use this bis-amine for cyclization[13] with CS_2 to (e)-(nido-carboranyl)-2-thio-hexahydro-[1,3]-diazepine [14] (11) (Scheme 3). The apparently rather strong inner-salt formation between the nido-carborate

and the attached amino group necessitates the use of a strong base like NaH and a high temperature to convert the ammonium salt to its neutral form.

Reactions with KOH in EtOH and NaH in THF were not successful in converting the starting material; only with NaH in DMF could the desired product be obtained.

Preliminary experiments showed that these compounds allowed selective uptake of boron in experimental melanoma of the mouse, though not to the same degree as the above-mentioned dihydroxyboryl derivatives.

Scheme 3:



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References and Notes

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1. D. Gabel and L.E. Feinendegen, Strahlenther. Onkol. 1989, 165, 65.

2. A.H. Soloway, F. Alam, R.F. Barth, and B.V. Bapat, Strahlenther. Onkol. 1989, 165, 118.

3. M.F. Hawthorne, D.C. Young, P.M. Garrett, D.A. Owen, S.G. Schwerin, F.N. Tebbe, and P.A. Wegner, J. Am. Chem. Soc 1967, 90, 862.

4. R.G. Fairchild, S. Packer, D. Greenberg, P. Som, A.B. Brill, I. Fand and W.P. McNally, Cancer Res. 1982, 42, 5126.

5. W. Tjarks and D. Gabel, submitted for publication.

6. To 6.4 g (50 mmol) 4-thiouracil (1) and 2 g (50 mmol) NaOH in 300 ml EtOH were added 15.6 g (50 mmol) 1-(3-iodopropyl)-o-carborane dissolved in 100 ml EtOH, and refluxed for 4 h. The solvent was evaporated, dissolved in ethyl acetate and extracted with 1 M HCl. After drying, the residue of the organic phase was chromatographed on SiO_2 in CH_2Cl_2 (9)/petrol ether (1). Yield 8.3 g = 53%, white crystals, mp 167-169 °C.
(2) was treated with $POCl_3$ to 3 (yield 89%, mp 91-93 °C) and further to 4 in refluxing EtOH with a 2-fold excess of thiourea. After evaporation of the majority of the solvent, 2 M NaOH was added and the solution was carefully acidified with HCl. The resulting precipitate was chromatographed on SiO_2 (CH_2Cl_2 9/MeOH 1) to yield 70% (4) in yellowish crystals. Analytical data of (4): mp 159-161 °C; MS (EI) 328 (M^+) (Here and in all boron-containing compounds, the mass of the most intense of the isotope pattern is indicated. The measured patterns agreed with the theoretical ones); IR (KBr) 3050 cm^{-1} ($C-H_{carborane}$), 2910, 2750 ($C-H_{aliph.}$), 2570 (B-H), 1530, 1510 (C=C, C=N); ^{1}H-NMR (DMSO-d_6) δ (ppm) 1.2-3.0 (br, m, 10 H, B-H), 1.74-1.83 (m, 2 H, $-CH_2-$), 2.33-2.47 (m, 2 H, $-CH_2$-carborane), 3.10-3.16 (t, 2 H, S-CH_2), 5.23 (s, 1 H, $C_{carborane}-H$), 6.73-6.78 (d, 1 H, C_5-H), 7.65-7.70 (d, 1 H, C_6-H)

7. Y. Mizuno, M. Ikehara, and K.A. Watanabe, Chem. Pharm. Bull. 1962, 10, 647.

8. (4) (1.64 g = 5 mmol) was added under nitrogen to 1.4 g (12.5 mmol) KOH in 50 ml MeOH. The solution was refluxed for 24 h. Excess KOH was precipitated by blowing CO_2 through the solution. The residue obtained after filtration and evaporation was washed with diethyl ether and dried. Yellow crystals, yield 41%. Analytical data: mp > 250 °C. MS (FAB$^-$, glycerol) 340 (M+Na-H)$^-$, 318 (M$^-$); IR (KBr) 2505 cm^{-1} (B-H), 1200 (C=S); ^{1}H-NMR (DMSO-d_6) (-3.20)-(-2.50) (d, br, 1 H, B-H$_{extra}$), (-0.75)-2.50 (m, br, 9 H, B-H), 1.45-1.78 (m, 5 H, -CH_2-CH_2-, C$_{carborane}$-H), 2.91-3.06 (m, 2 H, S-CH_2), 6.51-6.53 (d, 1 H, C_5-H), 7-66-7.69 (d. 1 H, C_6-H).

9. 2.4 g (8.2 mmol) (7) was suspended in 125 ml of a 10% aqueous solution of Na_2CO_3 and heated slowly to around 60 °C. When the solution clarified, heating was interrupted, and the solution was cooled. The resulting precipitate was filtered, washed with water, dissolved in EtOH, filtered, and evaporated. The product was purified chromatography on SiO_2 ($CHCl_3$ 20/MeOH 3). White plates, yield 76%. Analytical data: mp > 235 °C. MS (EI) 271 (M$^+$); IR (KBr) 2930 (C-H), 2580 (B-H), 1570 (amide); ^{1}H-NMR (DMSO-d_6) 1.1-3.2 (br, 10 H, B-H), 3.40 (s, 3 H, CH_3), 3.90 (s, 2 H, -CH_2-), 5.35 (s, 1 H, C$_{carborane}$-H), 13.88 (s, 1 H, N-H).

10. o-Carboranylacetyl chloride (6) (3.7 g = 0.017 mol) was dissolved in 20 ml dry 1,4-dioxane and added to 4.4 g (0.042 Mol) 4-methyl-3-thiosemicarbazide in 190 ml dry dioxane at 30 °C. Stirring was continued for 3 h. The solution was filtered and freed from solvent. Water was added, and the solution was extracted with diethyl ether. The residue obtained after evaropation of the solvent was washed with a small amount of ether. White crystals, yield 73%. Analytical data: mp 206 °C. MS (EI) 289 (M-H)$^+$); IR (KBr) 2940 (CH), 2600 (BH), 1700, 1560 (amide); ^{1}H-NMR (DMSO-d_6) 1.1-3.5 (br, 10 H, B-H), 2.85 (d, 3 H, -CH_3, 3.15 (s, 2 H, -CH_2-), 5.09 (s, 1 H, C$_{carborane}$-H), 7.90 (s, 1 H, N-H), 9.33 (s, 1 H, N-H), 10.05 (s, 1 H, N-H).

11. Prepared in analogy to (5). White crystals, yield 91%. Analytical Data: mp > 235 °C. MS (FAB$^-$, glycerol) 299 (M$^-$); ^{1}H-NMR (D_2O) (-3.3) (br, 1 H, H$_{extra}$), (-0.6)-2.6 (br, 9 H, B-H), 2.07 (s, 1 H, C$_{carborane}$-H), 3.07 (dd, 2 H, -CH_2), 3.49 (s, 3 H, -CH_3); IR (KBr) 3070, 2970 (C-H), 2550 (B-H).

12. L.I. Zakharkin, Yu. A. Chapovskii, V.A. Brattsev, and V.I. Stanko, J. Gen. Chem. USSR 1966, 36, 892. We used $SOCl_2$ instead of PCl_5.

13. S. Chau-Der Li, S.L. Mella, and A.C. Sartorelli, J. Med. Chem. 1981, 24, 1089.

14. (10) (0.5 g = 2.6 mmol) was dissolved in 10 ml freshly distilled, anhydrous N,N-dimethylformamide and added dropwise to a solution of 0.1 g (2.6 mmol) NaH (60% in mineral oil) in the same solvent, cooled to 0 °C. After 15 min, 0.18 ml (3 mmol) CS_2 were added, and the solution heated to 90 °C. After 1 h, 0.2 ml conc. HCl was added and stirring at this temperature was continued for 17 h. After cooling and filtering, the solution was evaporated. The resulting yellow oil was recrystallized twice from 20 ml water. White crystals (dimethylammonium salt), yield 33%. Analytical data: mp 185 °C. MS (FAB$^-$, glycerol) 233 (M-H)$^-$; IR (KBr) 3370, 3150 (NH), 2500 (BH); ^{1}H-NMR (DMSO-d_6) (-2.30)-(-2.10) (br, 1 H, B-H$_{extra}$), (-0.7)-2.5 (br, 9 H, B-H), 2.55 (s, 6 H, -CH_3), 2.90 (m, 2 H, -CH_2), 3.76 (m, 2 H, -CH_2), 7.89 (m, 1 H, S-H), 8.19 (br, 1 H, N-H).

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