SYNTHESIS OF *o*-CARBORANYLMETHYL ETHERS OF STEROIDS AS POTENTIAL TARGET SUBSTRATES FOR BORON NEUTRON CAPTURE THERAPY

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Received March 14, 1991
Accepted July 1, 1991

o-Carboranylmethyl ethers of steroids were synthesized by insertion of steroidal 2-propynyloxy derivatives into 6,9-bis(acetonitrile)decaborane (12). This reaction afforded compounds with estrane and androstane skeleton, potentionally useful in boron neutron capture therapy of hormone-sensitive forms of cancer: 17β-*o*-carboranylmethyl ether of estradiol *IXb* (yield 14%) and 3β- and 17β-carboranylmethyl ethers of androstenediol *Vb* and *VIIb* (yield 12% and 13%, respectively). Jones oxidation afforded carboranyl derivative of androsten-17-one *VIb* in 75% yield. As shown by a study of insertion of 3β-(2-propynyloxy)cholest-5-ene (*IVa*), the low yields of the insertion reaction cannot be increased by change in the reaction conditions. The relative binding affinity of compound *IXb* to estrogen receptor from rat uterine and human breast tumor cytosol was 3·0 and 0·29% respectively, of that of estradiol.

The use of *o*-carborane derivatives of steroidal hormones in the Boron Neutron Capture Therapy (BNCT) of hormone-sensitive cancer has been first suggested by Soloway[1] in the mid-sixties. Since then, several *o*-carborane steroidal derivatives[2-8] were prepared and the biochemical as well as biological activity of some of them has been studied[2,3,8]. Three different approaches have been used for the preparation of such compounds: 1) Insertion of acetylenic derivatives of steroids into *nido*-decaborane(14) in the presence of a Lewis base or into its 6,9-donor-acceptor complexes with Lewis bases[2-4,7,8], 2) reaction of *o*-carborane monolithium derivative with a suitable functional group (e.g. aldehyde, acyl chloride or oxirane) of the steroid[5,6], and 3) esterification of the hydroxy group of the steroid with carboranyl acyl chloride[5].

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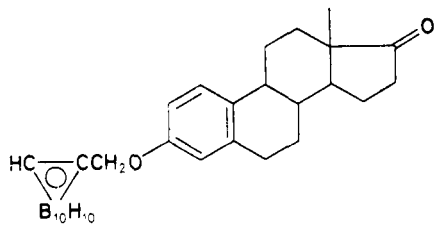
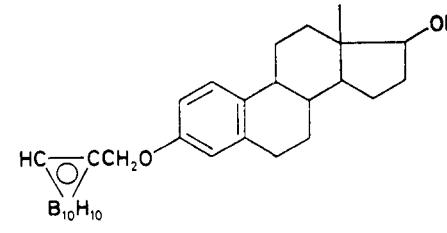
The *o*-carbonylmethyl ether of estrone, 3-(1-*o*-carboranylmethyloxy)estra-1,3,5(10)--trien-17-one (*I*), was prepared by Sweet[2] by the insertion reaction. He reduced this compound with sodium borohydride to the stable 3-(1-*o*-carboranylmethoxy)estra--1,3,5(10)-trien-17β-ol (*II*) which in short term administration did not appear to be toxic and was sufficiently stable under physiological conditions[2]. In the case of estradiol, however, the bulky substituent in position 3 reduces markedly the affinity of the *o*-carboranyl derivative *II* toward the estrogen receptors in the cell cytoplasm. The relative receptor binding activity (RBA) constant amounts to only 0·5%, related to 100% for estradiol[2]. On the other hand, estradiol substituted with *o*-carborane in the 17α-position, 17α-(1-*o*-carboranyl)estra-1,3,5(10)-triene-3,17β-diol (*III*), exhibits a biological activity comparable with that of the estradiol[3] itself. Similarly, for androgens the literature[9] stresses the importance of substitution and stereochemistry of the ring D and thus binding of a strongly hydrophobic *o*-carboranyl group via an ether bond directly in the 17β-position of the steroid may be expected to reduce the receptor activity[10].



I



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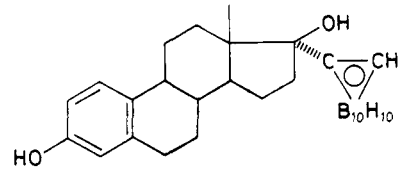


III

The present study is aimed at the preparation of new 1-*o*-carboranyl derivatives of estrogen and androgen type in which the *o*-carboranylmethyl group is bonded by an ether bond in position 3β and 17β. Particular attention was paid to the direct insertion of 2-propynyloxy steroidal derivatives[2] into *nido*-decaborane(14) in the presence of a basic solvent or its 6,9-bis(ligando)derivatives with Lewis bases and utilization of this reaction for the synthesis of *o*-carborane substituted steroids. The preparation of 2-propynyloxy derivatives of steroid hormones used for this insertion has been recently described[11–14].

Preliminary experiments studying the effect of reaction conditions (solvent, ligands or Lewis bases diethyl sulfide and acetonitrile, and the ratio of the reactants) were performed with 3β-(2-propynyloxy)cholest-5-ene (*IVa*) as the most accessible[11] of the propynyl derivatives. The highest yield of the desired product, 3β-(1-(1,2-dicarba--*closo*-dodecaboran(12))yl-methoxy)cholest-5-ene (*IVb*) was achieved in reaction of in situ prepared 6,9-bis(acetonitrile)decaborane(12) with compound *IVa* in boiling acetonitrile; also the purity of the thus-prepared compound was highest. Therefore, these conditions were also used in the preparation of all the other compounds. The structure of compound *IVb* was suggested on the basis of spectral measurements. Its IR spectrum exhibits a band at 2 595 cm^{-1} due to the B—H bond of the carborane moiety; on the other hand, bands characteristic of a terminal triple bond (3 310 and 2 120 cm^{-1}; cf. ref.[11]) are missing. The ^1H NMR spectrum displays a signal of proton bonded to carbon atom of the carborane skeleton (δ 3·94 ppm, see Table I). The ^{11}B NMR spectrum contains characteristic signals of *o*-carborane substituted with alkoxy group in position 1; for comparison we are listing shifts of signals for *o*-carborane with an ethoxy group in position 1: 5·52, −12·85, −13·34, −14·42, and −15·97 ppm (ref.[15]). The spectrum did not exhibit upfield signals which would correspond to possible impurities with the *nido*-skeleton such as 6,9-bis(acetonitrile)-decaborane[16] (δ −31·2 and −42·8 ppm). Mass spectrum of compound *IVb* displays molecular ions corresponding to the content of boron atoms in the molecule. The structure of all the *o*-carboranyl derivatives described below has been determined analogously. The final proof of the structure of compound *IVb* was obtained from the X-ray analysis[17].

TABLE I

^1H NMR spectral parameters of *o*-carborane derivatives in deuteriochloroform (for other conditions see Experimental)

Compound	H-18 s, 3 H	H-19 s, 3 H	H-3α m, 1 H	H-6 bd, 1 H	H-17α bt, 1 H	$-OCH_2$ s, 2 H	C—H[a] m, 1 H
IVb	0·67	0·99	3·15[b]	5·32[c]	[d]	3·88	3·94
Vb	0·76	1·00	3·13[b]	5·31[c]	3·64[c]	3·89	3·96
VIb	0·88	1·02	3·17	5·37[c]	—	3·88	3·94
VIIb	0·74	1·01	3·47	5·32[c]	3·32[c]	3·85	3·90
VIIIb	0·67	1·01	3·30[f]	5·33[c]	[d]	3·87	3·92
IXb[g]	0·76	—	—	[d]	3·37[h]	3·87	3·92

[a] Carborane proton; [b] $W = 34$; [c] $J \approx 4{\cdot}5$; [d] undeterminable value; [e] $J \approx 7$; [f] overlapped with other signal 2 × H-20; [g] other signals: 4·54 bs, 1 H (OH), 6·61 m and 7·12 m, 3 H (H-1, H-2, H-4); [h] $J \approx 8$.

Already preliminary attempts to insert 3β-(2-propynyloxy)cholest-5-ene (*IVa*) into 6,9-bis(acetonitrile)decaborane(12) have shown that the triple bond which is sterically hindered by the bulky steroid molecule reacts substantially less easily than that in aliphatic alkynes (cf. ref.[18]). To proceed successfully, the reaction requires refluxing the 2-propynyloxy derivative with 6,9-bis(ligando) derivative of decaborane(14) in a suitable solvent (acetonitrile, benzene, toluene or their mixtures). To achieve higher yield of the desired *o*-carboranyl derivatives of steroids, the reaction equilibrium was shifted to the product side using an excess of 6,9-bis(diethyl-sulfide)-*nido*-decaborane(12) or 6,9-bis(acetonitrile)-*nido*-decaborane(12). However, under such conditions undesired side reactions take place leading to many side products, obviously degradation products from 6,9-bis(ligando) derivative of decaborane(14) or *o*-carborane. Very often the solubility of these products is similar to that of the steroidal derivatives with strongly hydrophobic *o*-carborane moiety (limited to solvents of low polarity) and their decomposition to boric acid is not facile. Also their chromatographic behaviour on silica gel in the usual solvent systems (e.g. hexane–ether, hexane–2-propanol, hexane–ethyl acetate) is often very similar. Since it was necessary to separate complex mixtures and verify the purity of the prepared compounds, we studied the solubility of *o*-carboranyl-substituted steroids and their TLC in various solvent systems (Table II).

Insertion of 3β-(2-propynyloxy)androst-5-en-17β-ol (*Va*) into 6,9-bis(acetonitrile)-decaborane(12) afforded 3β-(1-(1,2-dicarba-*closo*-dodecaboran(12))yl-methoxy)androst-5-en-17β-ol (*Vb*). Compound *Vb* was obtained also in the attempted insertion of 3β-(2-propynyloxy)androst-5-en-17-one (*VIa*) into 6,9-bis(acetonitrile)decaborane-(12). In the course of the reaction the 17-keto group of the steroid was reduced by the hydride hydrogen of decaborane(14) or its degradation products, or of the

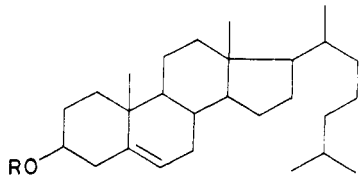
TABLE II

R_F values for *o*-carboranyl derivatives of steroids on Silufol (for other conditions see Experimental)

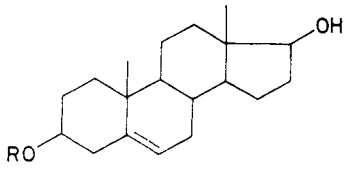
Compound	S1	S2	S3	S4	S5	S6	S7
IVb	0·15	[a]	≈1	0·43	0·71	0·70	0·78
Vb	≈0	[a]	0·07	0·51	0·15	0·24	0·78
VIb	[a]	0·45	0·20	[a]	0·46	0·79	[a]
VIIb	≈0	0·55	0·29	0·55	0·13	0·19	0·75
VIIIb	[a]	0·14	0·11	[a]	0·18	0·79	[a]
IXb	[a]	0·39	0·23	[a]	0·38	0·46	[a]

[a] The value was not determined.

o-carborane degradation products. Therefore, we prepared compound *VIb* by oxidation of the 17β-OH group in compound *Vb* with Jones reagent.



IV



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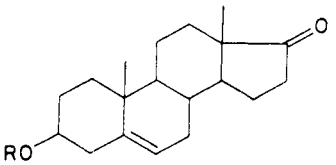
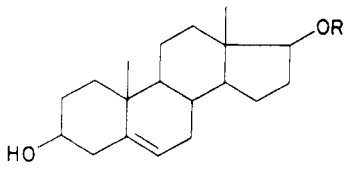
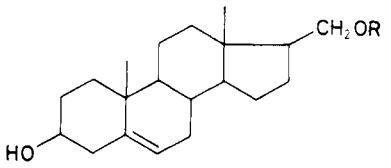


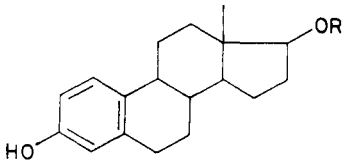
VI



VII



VIII



IX

In formulae *IV*–*IX*: *a*, R = $-CH_2C{\equiv}CH$; *b*, R = $-CH_2C(C_2B_{10}H_{10})CH$

By direct insertion of acetylenic steroidal derivatives *VIIa*, *VIIIa* and *IXa* we synthesized the respective *o*-carboranyl derivatives *VIIb*, *VIIIb* and *IXb*. The latter compound is regioisomeric to compound *II* in which the *o*-carboranyl group is attached by an ether bond to the 3β-position of the steroid[2]. The boron-estrogen derivative *IXb* has been tested for its specific binding to estrogen receptor from both rat uterine and human breast tumor cytosol. The relative binding affinity to the receptors was only 3·0 and 0·29% respectively, of that of estradiol. The detailed description of biological activity has been presented elsewhere[19].

EXPERIMENTAL

Melting points were determined on a Boetius block. Infrared spectra were measured on a Perkin–Elmer 580 spectrometer (wavenumbers in cm^{-1}). The ^1H NMR spectra were taken on a Tesla BS-497 instrument (FT mode, 100 MHz) at 23°C in deuteriochloroform with tetramethylsilane as internal standard. ^{11}B NMR spectra were obtained with a Varian XL-200 spectrometer (FT mode, 64·184 MHz) in hexadeuterioacetone with boron trifluoride etherate as external standard; chemical shifts are given in ppm (δ-scale), coupling constants (J) and bandwidths (W) in Hz. Preparative thin-layer chromatography was performed on silica gel G (Lachema) or silica gel G (Merck) with a UV-indicator. TLC of steroidal *o*-carboranyl derivatives was carried out on Silufol sheets. Spots were detected by spraying with: 1) 5% $AgNO_3$ solution – the undesired boron hydrides with an open skeleton afforded a brown to brown-black coloured spots; 2) concentrated sulfuric acid; on heating *o*-carboranyl and propynyloxy derivatives of steroids afforded a blue to violet colouration. As solvent systems were used: S1 hexane–chloroform (9 : 1), S2 hexane–benzene (1 : 9), S3 hexane–ethyl acetate (85 : 15), S4 hexane–methanol (5 : 95), S5 benzene–ether (9 : 1), S6 benzene–ethyl acetate (9 : 1), S7 dichloromethane–acetonitrile (8 : 2). In the preparative TLC the compounds were detected by UV-light (360 nm) after spraying with 1% methanolic solution of morin. Column chromatography was carried out on silica gel (60 μm, Lachema). Solutions in organic solvents were dried over anhydrous sodium sulfate and the solvents were evaporated on a rotatory evaporator at about 2 kPa. Analytical samples were dried for 12 h over phosphorus pentoxide at 40°C/26 Pa. *nido*-Decaborane(14) was purified by sublimation under diminished pressure (26 Pa) prior to use.

3β-(1-(1,2-Dicarba-*closo*-dodecaborane(12))yl-methoxy)cholest-5-ene (*IVb*)

A) A mixture of compound *IVa* (258 mg, 0·61 mmol), acetonitrile (30 ml) and *nido*-decaborane-(14) (1·1 g, 9·2 mmol) was refluxed under nitrogen for 7·5 h. After cooling, the solution was filtered and the solvent was evaporated in vacuo. The residue was taken up in boiling cyclohexane (3 × 20 ml), the combined organic phases were evaporated in vacuo and the remaining solid was refluxed with methanol (10 ml) for 30 min. After cooling, the solid crude product was collected, crystallized from hexane and purified by chromatography on 2 preparative plates of silica gel; yield 100 mg (30%) of product *IVb*, m.p. 226–229°C. Solubility: hexane, cyclohexane, chloroform, ether – good; acetonitrile, methanol, ethanol – poor. IR spectrum (tetrachloromethane): 3 090 (C—H, carborane); 2 595 (B—H); 1 668 (C=C). ^{11}B NMR spectrum: −4·29 d (B-9); −5·89 d (B-12); −10·13 d (B-8, B-10); −12·66 m and −14·03 m (B-3, B-4, B-5, B-6, B-7, B-10). Mass spectrum, m/z (intensity %): 545 (19), 544 (56), 543 (100), 542 (90), (M^+ $C_{30}H_{58}$·.$B_{10}O$).

B) A mixture of compound *IVa* (448 mg, 1·05 mmol), 6,9-bis(diethylsulfide)decaborane(12) (1·046 g, 5 mmol) and toluene (20 ml) was refluxed for 8 h. After removal of the solvent in vacuo, the residue was refluxed with a mixture of methanol (20 ml) and aqueous ammonia (6 ml) for 1 h. The solvents were evaporated, the product was dissolved in hot hexane (30 ml), the hot solution was filtered and the cold filtrate was washed with water (3 × 10 ml). After drying, the solution was concentrated to a small volume, the separated product was filtered and purified on 4 preparative plates of silica gel (240 × 90 × 0·7 mm) in benzene–hexane (2 : 1). Yield 110 mg (20%) of product *IVb*, identical with the product prepared by procedure *A*.

3β-(1-(1,2-Dicarba-*closo*-dodecaborane(12))yl-methoxy)androst-5-en-17β-ol (*Vb*)

A) A mixture of ketone *VIa* (1·76 g, 5·4 mmol), 6,9-bis(acetonitrile)-*nido*-decaborane(12) (3·72 g, 13·4 mmol), acetonitrile (30 ml) and benzene (10 ml) was refluxed under nitrogen for

4·5 h. After cooling, the mixture was filtered and the solvents were evaporated. The residue was refluxed with 3% methanolic ammonia (20 ml) for 75 min, the solvent was evaporated and the residue was crystallized from hexane–ether (1 : 2). The obtained crude product was chromatographed on a column of silica gel (50 g) in hexane–ether (2 : 3) to afford 283 mg of product *Vb*. Preparative TLC of the intermediate fraction (33 mg) on silica gel in ether gave further 11 mg of the product; total yield of *Vb* was 294 mg (12%); m.p. 234–236°C. Solubility: hexane, cyclohexane, acetonitrile, methanol, ethanol – poor; ether – good. IR spectrum (chloroform): 3 615 (O—H); 2 595 (B—H); 1 668 (C=C). ^{11}B NMR spectrum: −4·26 d (B-9); −6·08 d (B-12); −10·17 d (B-8, B-10); −12·68 m and −14·21 m (B-3, B-4, B-5, B-6, B-7, B-11). Mass spectrum, *m/z* (intensity %): 448 (36), 447 (87), 446 (100), 445 (37), (M^+ $C_{22}H_{42}B_{10}O_2$).

B) A mixture of compound *Va* (394 mg, 1·2 mmol), 6,9-bis(diethylsulfide)-*nido*-decaborane(12) (690 mg, 3·5 mmol) and acetonitrile (30 ml) was refluxed under nitrogen for 8 h. The solvent was then evaporated in vacuo and the residue was refluxed with 50% aqueous methanol (30 ml) under nitrogen for 2 h. The product was filtered and partitioned between benzene and water (3× between 20 ml and 20 ml). The combined organic phases were filtered through a column of silica gel layered with anhydrous sodium sulfate. After removal of benzene in vacuo, the crude product was purified by crystallization from hexane–ether and further by preparative TLC on silica gel (2 plates) in hexane–ether (4 : 6). Yield 60 mg (11%) of product *Vb*, identical with the product prepared by procedure *A*.

3β-(1-(1,2-Dicarba-*closo*-dodecaboran(12))yl-methoxy)androst-5-en-17-one (*VIb*)

Hydroxy derivative *Vb* (240 mg, 0·73 mmol) was dissolved under nitrogen in boiling acetone (20 ml). After cooling to room temperature, Jones reagent was added dropwise to the solution until the green colouration of the reaction mixture had a permanent orange shade. The reaction mixture was partitioned between ether and water and the ethereal phase was washed with aqueous solution of potassium hydrogen carbonate and ammonium sulfate (3×). After drying and evaporation of the solvent, the residue was crystallized from chloroform, affording 175 mg (73%) of compound *VIb*, m.p. 225–230°C. Solubility: hexane, cyclohexane, acetonitrile, methanol, ethanol – poor; ether – good. IR spectrum (chloroform): 2 590 (B—H); 1 735 (C=O); 1 669 (C=C); 1 115 (C—O). ^{11}B NMR spectrum: −4·27 d (B-9); −6·08 d (B-12); −10·17 d (B-8, B-10); −12·67 m and −14·24 m (B-3, B-4, B-5, B-6, B-7, B-11). Mass spectrum, *m/z* (intensity %): 446 (47), 445 (99), 444 (100), 443 (64), 442 (25). (M^+ $C_{22}H_{40}B_{10}O_2$).

17β-(1-(1,2-Dicarba-*closo*-dodecaboran(12))yl-methoxy)androst-5-en-3β-ol (*VIIb*)

A mixture of compound *VIIa* (960 mg, 2·9 mmol), 6,9-bis(acetonitrile)-*nido*-decaborane(12) (2·03 g, 10·3 mmol), acetonitrile (35 ml) and benzene (10 ml) was refluxed under nitrogen for 9 h. The solvent was evaporated in vacuo and the residue was refluxed with benzene (30 ml) and triethylamine (10 ml) for 30 min. The orange precipitate was filtered and extracted with boiling hexane (3 × 20 ml). Evaporation of the hexane extract in vacuo afforded the crude product which was further purified by preparative TLC on silica gel (6 plates) in hexane–ethyl acetate (8 : 2). Yield 270 mg (10%) of product *VIIb*, m.p. 159–162°C. Solubility: hexane, cyclohexane, methanol, ethanol ether – poor; acetonitrile – good. IR spectrum (chloroform): 3 610 (O—H); 2 590 (B—H); 1 670 (C=C). ^{11}B NMR spectrum: −4·29 d (B-9); −5·81 d (B-12); −10·18 d (B-8, B-10); −12·73 m and −14·30 m (B-3, B-4, B-5, B-6, B-7, B-11). Mass spectrum, *m/z* (intensity %): 448 (61), 447 (97), 446 (100), 445 (73), 444 (22), (M^+ $C_{22}H_{42}B_{10}O_2$).

20-(1-(1,2-Dicarba-*closo*-dodecaboran(12))yl-methoxy)-
-21-norpregn-5-en-3β-ol (*VIIIb*)

A mixture of compound *VIIIa* (1·03 g, 3·0 mmol), 6,9-bis(acetonitrile)-*nido*-decaborane(12) (1·04 g, 5·1 mmol), acetonitrile (40 ml) and benzene (5 ml) was refluxed under nitrogen for 6 h. The solvent was evaporated in vacuo and the residue was mixed with methanol (10 ml). The methanol, together with methyl borate, was distilled off in vacuo and the solid residue was washed with boiling hexane (3 × 20 ml). The insoluble material was dissolved in ether and chromatographed on silica gel (4 preparative plates) in tetrachloromethane–acetonitrile (8 : 2), affording 100 mg (7·2%) of amorphous product *VIIIb*. Solubility: hexane, cyclohexane, acetonitrile, methanol, ethanol — poor; ether — good. IR spectrum (chloroform): 3 610 (O—H); 2 590 (B—H); 1 668 (C=C); 1 126, 1 046 (C—O). Mass spectrum, *m/z* (intensity %): 462 (59), 461 (100), 460 (96), 459 (58), 458 (23) (M^+, $C_{23}H_{44}B_{10}O_2$).

17β-(1-(1,2-Dicarba-*closo*-dodecaboran(12))yl-methoxy)estra-1,3,5(10)-trien-3-ol (*IXb*)

A mixture of compound *IXa* (686 mg, 2·2 mmol), 6,9-bis(acetonitrile)-*nido*-decaborane(12) (1·86 g, 9·2 mmol), acetonitrile (30 ml) and benzene (10 ml) was refluxed under nitrogen for 11 h. The solvent was evaporated in vacuo and the residue was refluxed with methanol (30 ml) for 2·5 h. After evaporation of methanol the remaining solid was mixed with ether (20 ml) and methanol was added dropwise until all the material dissolved. The ethereal phase was washed with water (20 ml) and the aqueous one was extracted with ether (2 × 10 ml). The combined ethereal phases were evaporated in vacuo and the residue was dissolved in hexane–ethyl acetate (8 : 2) and chromatographed in the same solvent mixture on a column of silica gel (100 g). The crude product was further purified by preparative TLC on silica gel (3 plates) in benzene–ethyl acetate (85 : 5) followed by crystallization from hexane–ether. Yield 136 mg (14%) of product *IXb*, m.p. 197—198°C. Solubility: hexane, cyclohexane, methanol, ethanol, ether — good. IR spectrum (chloroform): 3 600 (O—H); 2 600 (B—H); 1 610, 1 505 (arom); 1 140 (C—O). ^{11}B NMR spectrum: −4·25 d (B-9), −5·97 d (B-12), −10·15 d (B-8, B-10), −12·69 m and −14·22 m (B-3, B-4, B-5, B-6, B-7, B-11). Mass spectrum, *m/z* (intensity %): 430 (54), 429 (79), 428 (100), 427 (53) (M^+ $C_{21}H_{36}B_{10}O_2$).

Binding of Compound *IXb* to Estrogen Receptor

The relative binding affinity has been determined from the amounts of estradiol and the competitor, required to displace 50% of [^{3}H]estradiol from its binding to both rat uterine and human breast tumor cytosol. A procedure similar to that described by Grill et al.[20] has been used. In brief, increasing concentrations of estradiol (0·5—4 nmol l^{-1}) or of the competitor (1 to 64 nmol l^{-1}) (in each case four duplicate experimental points) were incubated in an ice bath for 3 h with a constant amount of [^{3}H]estradiol (specific activity 101 Ci . mol^{-1}, 33 000 d.p.m. per tube) and cytosol (binding capacity for estradiol 131 and 17·8 fmol . mg^{-1} total protein for rat and human preparation, respectively), with or without an excess (1 μmol . l^{-1}) of unlabelled estradiol, in final volume 0·3 ml. Bound and free ligands were separated by charcoal–dextran adsorption.

The authors are indebted to Dr S. Heřmánek, Institute of Inorganic Chemistry, Czechoslovak Academy of Sciences, Prague, for the measurements and interpretation of the ^{11}B NMR *spectra and to Dr J. Plešek and Dr B. Štíbr of the same Institute for valuable advice and comments. They also thank Mrs J. Jelínková and Mrs M. Snopková for measurements of* ^{1}H NMR *spectra, Dr S. Vašíčková for the* IR *spectra and Dr K. Ubik for the mass spectra (all of Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, Prague).*

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Translated by M. Tichý.