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Serendipitous oxidation product of BIBN4096BS: A potent CGRP receptor antagonist

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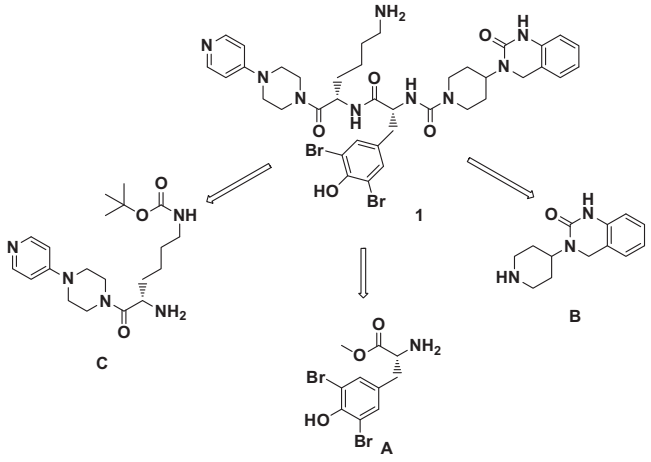
ABSTRACT

An oxidation product (**5**) formed during the synthesis of BIBN-4096BS (**1**) was found to be a potent CGRP antagonist (IC_{50} = 0.11 nM). While **5** was found to be ten-fold less potent than **1**, another analog **8** with lower molecular weight containing the oxidized fragment demonstrated twenty-fold higher activity than its parent **7**. Alternative conditions which preclude the formation of the oxidation product are described. The activities of **1**, **5**, **7** and **8** in functional cAMP assay are also discussed.

Migraines are episodic headaches often characterized by severe unilateral head pain, photophobia, phonophobia and nausea.[1] It has been hypothesized that migraines are associated with the dilation of cranial blood vessels and activation of the trigeminovascular system.[2] More recent thinking has focused on the importance of halting peripheral afferent sensitization as key to antimigraine efficacy,[3b] whereas others see blocking central sensitization as critical.[3c] Triptans, which are the current standard of care for migraines, are 5-$HT_{1B/1D}$ agonists and are believed to function by their active, nonselective vasoconstriction of these cranial vessels.[3a] However, because triptans are nonselective vasoconstrictors, they are also associated with a number of cardiovascular side effects and are contraindicated in patients with hypertension or ischemic heart disease.[1] Calcitonin gene-related peptide (CGRP), an extremely potent vasodilator, is believed to play an important role in the pathophysiology of migraine[4] as five different CGRP receptor antagonists have been shown to be effective anti-migraines agents in clinical trials.[5] CGRP binds to the CGRP receptor, which is a G-protein coupled component, calcitonin receptor-like receptor (CRLR), receptor consisting of a classical 7-transmembrane and a receptor activity modifying protein (RAMP).[6] Marked elevation of CGRP in serum has been detected in individuals diagnosed with migraine.[4f]

Treatment with anti-migraine drugs, such as sumatriptan returns CGRP levels to normal, coincident with the alleviation of headache.[7]

Several research groups have developed both peptidic and non-peptidic antagonists for the CGRP receptor.[8] It is interesting to note that a truncated form of CGRP [CGRP(8-37)] itself is a peptidic antagonist for the CGRP receptor.[9] This compound is potent (K_i = 3.2 nM), but it is rapidly degraded in human plasma ($t_{1/2}$ = 20 min) and not really suitable as a in vivo blocker of CGRP pharmacology.[8b] Recently BIBN4096BS (**1**)[10] was identified as a potent antagonist for human



Scheme 1. Retrosynthetic plan for synthesis of BIBN4096BS.

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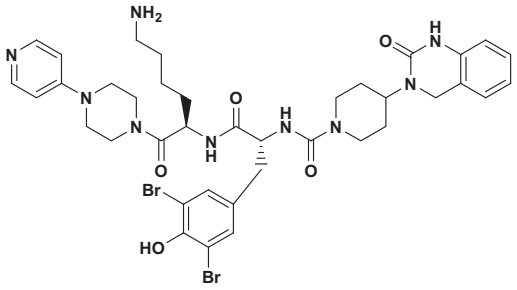
CGRP receptor. In binding assays using SK-N-MC cells, **1** demonstrated 150-fold greater affinity compared to that of the peptide antagonist CGRP(8-37).[10]

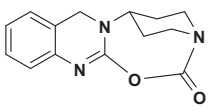
In our medicinal chemistry efforts, we engaged in a program toward the discovery of new CGRP receptor antagonists as potential therapeutics for the treatment of migraine.[11] Since **1** was a potent non-peptidic antagonist of CGRP receptor, we saw it as a starting point to understand the structural requirements for CGRP receptor antagonism. The synthesis of this molecule[12b] was non-trivial and care had to be exercised to avoid side reactions and racemization. In this communication, we report the identification of a benzylic oxidation product **5** (Scheme 3) formed unexpectedly during the synthesis of **1**. In vitro activity of the two compounds containing this benzylic oxidation fragment against CGRP receptor is also reported herein.



(1)

Even though BIBN-4096BS was largely prepared by the reported route, several interesting observations are worth noting. The strategy was to separately prepare the three key pieces (Scheme 1), and assemble them in a convergent synthesis. Since there were two chiral centers in the molecule prone to epimerization, mild reactions conditions had to be employed to preclude the possibility of racemization.

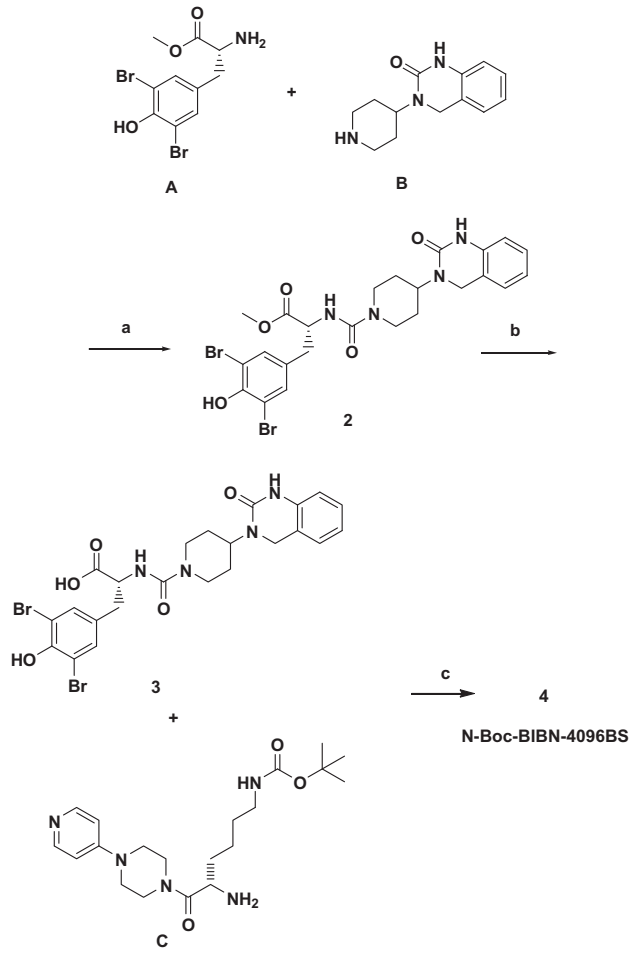
Initially, when we attempted to couple the pieces A and B using CDI and 1,2,4-triazole by mixing all the reagents together, the major product formed was not the desired product **2** (Scheme 2). Instead a cyclic urethane formed from 3-(piperidin-4-yl)-3,4-dihydroquinazolin-2-ol as shown below was the major product as evidenced by LC-MS.



cyclic urethane by LCMS

To avoid this undesired cyclization product during coupling with CDI, the tyrosine unit **A** was pretreated with CDI and 1,2,4-triazole, and then the dihydroquinolinone fragment **B** was added to obtain the desired product **2** (Scheme 2). The ester was then hydrolyzed to obtain carboxylic acid **3**, which after coupling with the L-lysine component **C** afforded N-Boc-protected BIBN-4096BS (**4**).

In the literature[12a] pertaining to analogs of **1**, two methods (HCl/dioxane or TFA/dichloromethane) were used for the removal of the N-Boc in **4**. When the N-Boc group on the lysine amine in **4** was removed by treatment with 4 M HCl in dioxane, reverse phase LC-MS analysis of the reaction mixture showed the desired BIBN4096BS (**1**) as the major product (31%) along with a minor product (12%), which eluted faster than the desired product. The minor product **5** had mass 14 units higher than **1**, suggesting oxidation of a methylene group. There were two benzylic positions in **1**, one located on the dibromotyrosine residue and the other on the 3,4-dihydroquinazilinone moiety. We wanted to determine of these two positions which one underwent oxidation, and the



Scheme 2. Coupling of components **A**, **B** and **C**. Reagents and conditions: (a) CDI, 1,2,4-triazole, DMF, 51%; (b) LiOH·H_2O, DME, H_2O, 40 °C, 79%; (c) TBTU, HOBt, DMF (crude, not purified at this stage).

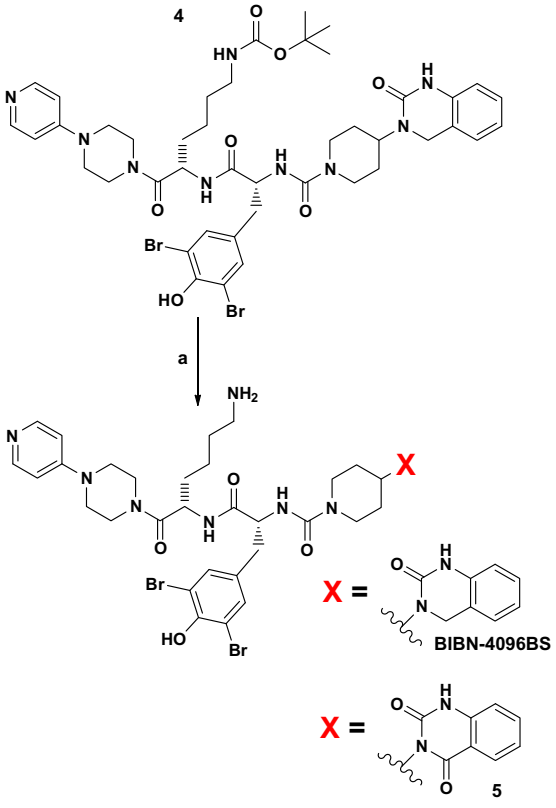
activity of the oxidation product as a CGRP antagonist. Based on NMR studies, the site of the oxidation was confirmed to be at the benzylic position of the 3,4-dihydroquinazoline moiety as shown in **5**.[14] A known peroxide contaminant in 1,4-dioxane is 2-hydroperoxy-1,4-dioxane. We speculate that a contaminant such as 2-hydroperoxy-1,4-dioxane provided the oxidant for converting **1** to **5**.

While the amount of oxidation product formed was only 12%, its formation as a byproduct in the final deprotection step and the difficulty of separating this byproduct from the required product prompted us to investigate this deprotection reaction further. To avoid the oxidation product, TFA and water mixture (90:10, 15 min, ambient temperature) was used for the N-Boc removal. Under these conditions, no benzylic oxidation product **5** was observed (Scheme 3).

The HPLC conditions for separation of BIBN-4096BS (**1**) and **5** and the HPLC traces are shown below in Figures 1 and 2.

We assessed the binding activity of this novel oxidation product on SK-N-MC membrane tissue (Fig. 3). Binding assays[13] were carried out with either ^{125}I-CGRP or ^{125}I-CGRP(8-37), using SK-N-MC membrane tissue. It was found that **5** (IC_{50} = 0.11 nM) was 10-fold less potent than **1** (IC_{50} = 0.014 nM) (Fig. 4).

Compounds **1** and **5** were also tested for their activity in a cAMP functional assay.[13] Compound **1** (EC_{50} = 0.026 nM) was 6-fold more active than **5** (EC_{50} = 0.15 nM). Nonetheless, the oxidized product **5** demonstrated sub-nanomolar activity as a CGRP receptor antagonist.



Scheme 3. N-Boc-deprotection conditions: (a) 4 M HCl in dioxane, CH_2Cl_2 (BIBN-4096BS, 31% yield; compound **5**, 12% yield).

We examined analogs of BIBN-4096BS (**1**) and its oxidation by-product (**5**) by replacing the dibromotyrosine in **1** with a simpler pharmacophore to see if these analogs could retain CGRP receptor antagonist activity (Scheme 4).[15] In compounds **7** and **8** the 3,5-dibromo-4-hydroxyphenyl residue present in **1** and **5** was replaced by a smaller benozothiophene unit, shown previously to be active in other CGRP receptor antagonists.[13b] The key intermediate **6** was prepared following similar procedure described for the synthesis of **1** (Scheme 4).[12a] In this case it was also found that HCl in dioxane also effected the benzylic oxidation side reaction.

Interestingly, when **7** and **8** were evaluated in our CGRP binding assay, the oxidized version **8** (IC_{50} = 2.7 nM) was found to be ten-fold more potent than **7** (IC_{50} = 25 nM) (Fig. 5).

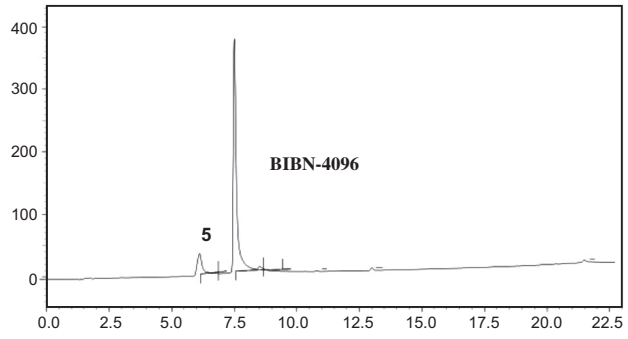


Figure 1. HPLC trace for BIBN-4096BS and **5**. YMC Xterra RP_{C18} column, 4.6 × 150 mm, 3.5 μm; A = 5 mM ammonium acetate/H_2O, pH 7.2; B = 5 mM ammonium acetate/10% H_2O/90% acetonitrile, pH 7.2; 15–80% B in 20 min, 3 min hold, @1.0 mL/min.

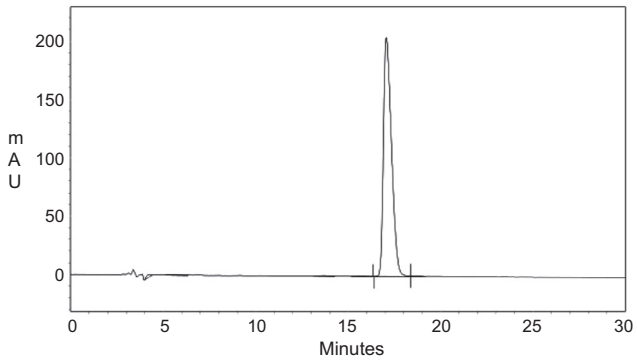


Figure 2. HPLC trace of BIBN4096BS. YMC Xterra RPC18 column, 4.6 × 150 mm, 10 μm; A = 0.05% TFA/H_2O; B = 0.05% TFA/acetonitrile; 25% B @0.5 mL/min. for 30 min.

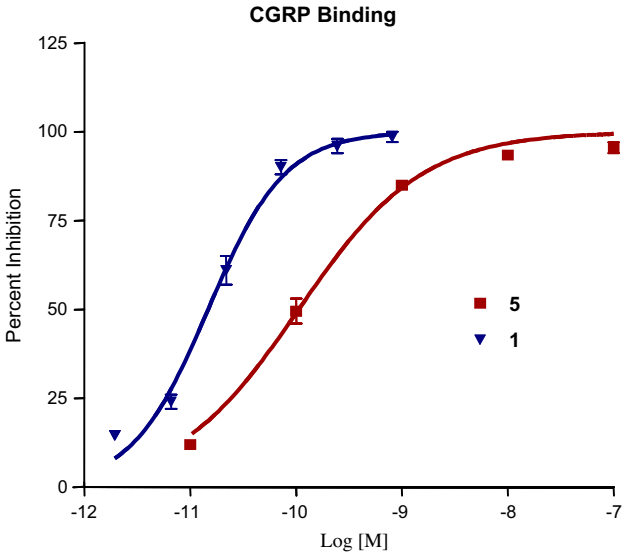


Figure 3. Percent of inhibition in ^{125}I-hCGRP binding assay—hCGRP1 receptor in SK-N-MC cells of **1** (BIBN4096BS) and **5**.

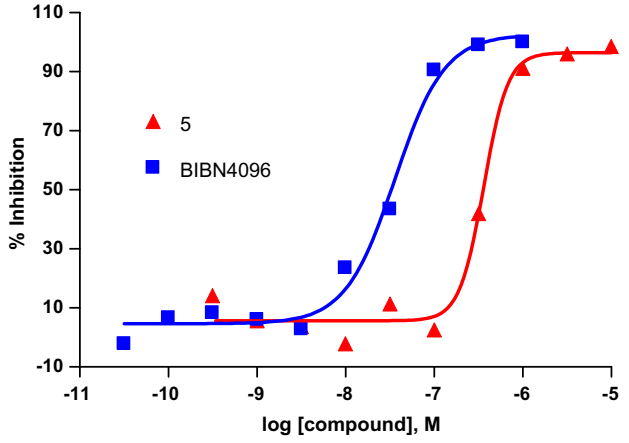
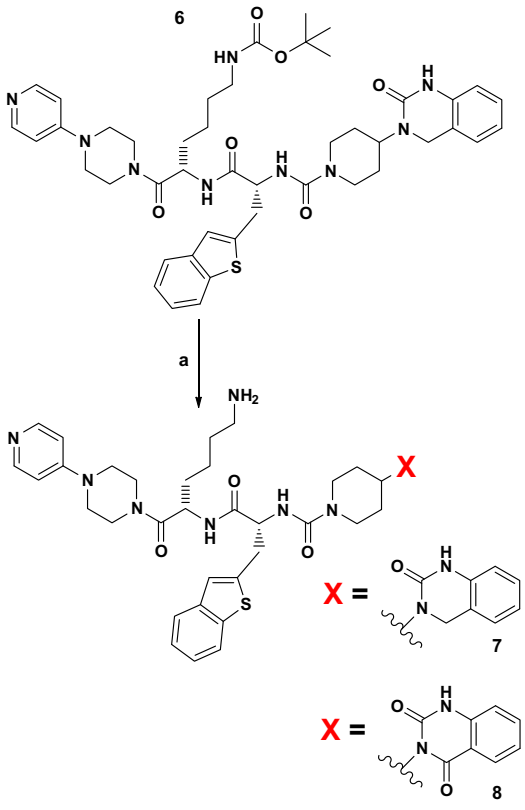


Figure 4. Percent of inhibition in CGRP1 receptor (SK-N-MC) cAMP assay—antagonism of 300 pM αCGRP of compounds **1** and **5**.



Scheme 4. N-Boc-deprotection conditions: (a) 4 M HCl in dioxane, CH_2Cl_2 (compound **7**, 19%; compound **8**, 41%).

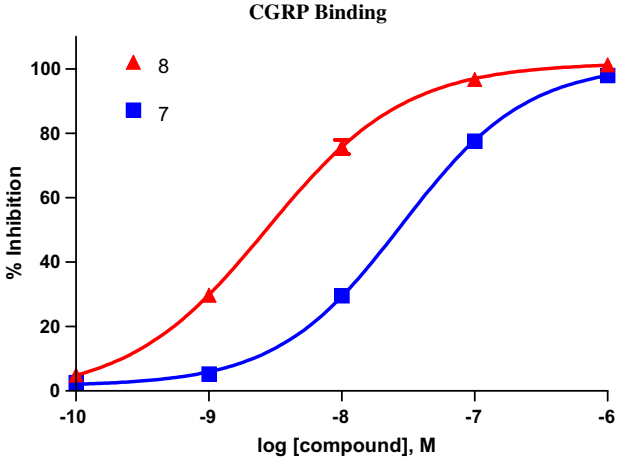


Figure 5. Percent of inhibition in ^{125}I-hCGRP binding assay—hCGRP1 receptor in SK-N-MC cells of compounds **7** and **8**.

Compounds **7** and **8** were also tested for activity in the cAMP functional assay (Fig. 6). Compound **7** (EC_{50} = 96 nM) and **8** (EC_{50} = 100 nM) showed equivalent activity showing that the oxidized compound **8** was equipotent with **7** as a CGRP receptor antagonist.

In conclusion, during the eleven step synthesis of **1** we identified a novel benzylic oxidation product **5** which was found to be a potent CGRP receptor antagonist. Alternative conditions (90% TFA, 10% water, ambient temperature) which abrogated such an oxidation were subsequently utilized. We synthesized **7** as an analog of **1** with a smaller side chain and were able to show that 7 and its oxidation analog **8** also were also both potent CGRP receptor antagonists.

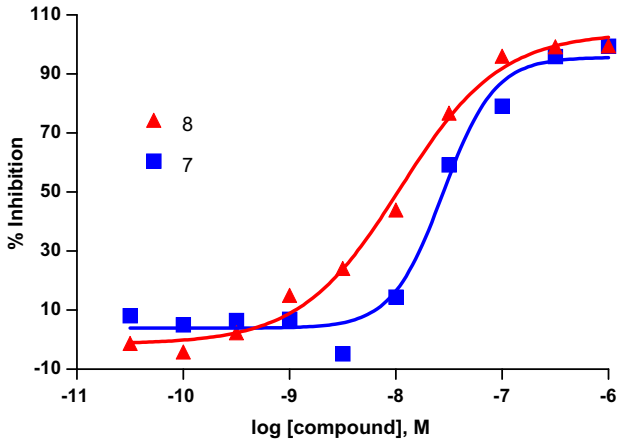


Figure 6. Percent of inhibition in CGRP1 receptor (SK-N-MC) cAMP assay—antagonism of 300 pM αCGRP of compounds **7** and **8**.

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14. ^{1}H NMR (500 MHz, *MeOD*) δ ppm: 8.13 (2H, d, J = 7.6 Hz), 8.01 (1H, d, J = 7.0 Hz), 7.61–7.67 (1H, m), 7.42–7.46 (2H, m), 7.22 (1H, s), 7.12–7.19 (3H, m), 5.01–5.12 (1H, m), 4.81 (1H, dd, J = 7.6, 6.10 Hz), 4.44 (1H, t, J = 7.8 Hz), 4.11–4.22 (2H, m), 3.96–4.06 (2H, m), 3.85–3.94 (2H, m), 3.69–3.82 (3H, m), 3.58–3.68 (1H, m), 2.84–3.04 (6H, m), 2.51–2.74 (2H, m), 1.52–1.85 (5H, m), 1.21–1.39 (3H, m); Also analyzed by COSY, HMQC and HMBC and NOSY NMR for structure elucidation; HRMS: $(M+H)^+$ 882.19; LC–MS: R_t = 1.36 min, $(M+H)^+$ 882.22 (method: 0–100% B, 2 min gradient, 3 min run (solvent A 90% water, 10% methanol, 0.1% TFA and solvent B, 10% water, 90% methanol and 0.1% TFA), λ 200 nM, flow 5 mL/min).
15. ^{1}H NMR (500 MHz, *MeOD*) δ ppm: 8.14 (2H, d, J = 7.3 Hz), 8.01 (1H, d, J = 7.02 Hz), 7.90 (2H, dd, J = 15.6, 7.9 Hz), 7.61–7.68 (1H, m), 7.40–7.48 (2H, m), 7.37 (1H, t, J = 7.2 Hz), 7.22 (1H, t, J = 7.5 Hz), 7.10–7.19 (3H, m), 5.00–5.11 (1H, m, J = 11.9, 7.97, 3.97, 3.97 Hz), 4.77 (1H, dd, J = 7.8, 5.9 Hz), 4.67 (1H, t, J = 7.6 Hz), 4.08–4.21 (2H, m), 3.93–4.03 (2H, m), 3.82–3.89 (2H, m), 3.67–3.79 (3H, m), 3.55–3.67 (1H, m), 3.44 (1H, dd, J = 14.3, 7.6 Hz), 3.28 (1H, dd, J = 14.5, 7.8 Hz), 2.81–2.93 (4H, m), 2.53–2.73 (2H, m), 1.54–1.72 (5H, m), 1.39–1.48 (1H, m), 1.15–1.25 (2H, m). MS: showed (M+H) peak at 766.5 and (M−H) peak at 764.4 (solvent: acetonitrile, water, TFA); LC–MS: R_t = 1.43 min, $(M+H)^+$ 766.42 [method: same as Ref. 13].