Some Stereochemical Aspects of the Strecker Synthesis and the Bucherer Bergs Reaction and the Crystal Structure of Racemic Bicyclo[2.2.1]heptane-2-*endo*-carboxylic acid-6-*spiro*-5'-hydantoin

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Abstract

Both the Strecker and Bucherer-Bergs reactions convert the norbornane keto-ester, methyl bicyclo[2.2.1]hept-6-one-2-*endo*-carboxylate into the lactam 6-*endo*-amino-bicyclo[2.2.1]heptane-2-*endo*-carboxylic acid- γ -lactam-6-*exo*-carboxylic acid. This lactam is unusually stable and cannot be hydrolysed to the corresponding amino acid. The stereochemistry in the case of the Strecker reaction, i.e. amino group *endo*, is contrary to that expected based on literature precedent. The stereochemistry in the case of the Bucherer-Bergs reaction, i.e. amino group *endo* has been confirmed by an X-ray crystallographic analysis on the intermediate spiro hydantoin ($\pm$)-bicyclo[2.2.1]heptane-2-*endo*-carboxylic acid-6-*spiro*-5'-hydantoin.

Introduction

Interest in the field of excitatory amino acid neurotransmitters, especially metabotropic glutamate receptor ligands, continues unabated.^[1-6]

As part of a programme concerned with the synthesis of conformationally rigid analogues of the neurotransmitter, L-glutamic acid, we wished to synthesise the glutamate analogues (1) and (2). Analogue (1) was of particular interest as it retains the carboxy and the amino functions in a 'folded' conformation, a conformation that has been suggested, is important for activity at the NMDA and the Kainate receptors.^[7]

Figure 1

Our approach to the synthesis of (1) and (2) is outlined in Scheme 1 below.

Scheme 1

Results and Discussion

The keto acid (7) was prepared via a Diels-Alder^[8] reaction between cyclopentadiene (3) and acrylic acid (4), followed by bromolactonisation,^[9] separation of the of the bromolactone (6) from the *exo* isomer of acid (5) and treatment of (6) with methanolic potassium hydroxide according to the literature procedure.^[10, 11]

Treatment of (7) with sodium cyanide, ammonium chloride and ammonia with methanol/water at 50°C for 5 hr (standard Strecker conditions)^[12] in an open vessel gave no reaction. This is

consistent with early reports that 2-norbornanone does not readily form amino nitriles and that more forcing conditions are required.^[13]

Repetition of the above procedure in a sealed vessel at 50°C for 5 hr gave the lactam (11, Scheme 2) in 25% overall yield. The procedure of Christensen and Tager^[13] was also tried, as this is reported to give superior yields with keto-acids.^[29] Following this procedure (using KCN instead of NaCN, omission of ammonia and performing the reaction at 80°C for 8hr), the reaction mixture was evaporated to dryness and the residue refluxed in conc. hydrochloric acid for 3hr,^[14] or alternatively, hydrolysed in a sealed vessel for 12hr at 124°C with 6M HCl.^[13] Upon cooling, the lactam (11) precipitated in analytically pure form. The yield (25%) was identical to that obtained using the sealed vessel Strecker procedure, and comparable to that reported^[13] for the Strecker reaction of 2-norbornanone. The structure of (11) was confirmed from the ¹H and the ¹³C-NMR {carbonyls at 180.14 ppm (acid) and 174.46 ppm (lactam)^[16]}, IR {3200 cm⁻¹ (NH)^[17] and 1640 cm⁻¹ (lactam carbonyl)^[17]}, ES-MS and microanalytical data. The lactam (11) was remarkably stable, and was recovered unchanged after refluxing in concentrated potassium hydroxide for 24 hr. In contrast, the 7-*syn* lactam (13) is formed under alkaline conditions and ring-opened under mild acidic hydrolysis conditions to form the corresponding amino acid together with a trace amount of C-7 epimerised product.^[18, 19]

Scheme 2

Apparently the lactam (11) is so stable^[29] that ring-opening, or epimerisation of the 2-*endo* carboxy group to the 2-*exo* carboxy group, is not competitive under the conditions of acid or base hydrolysis. The formation of the lactam (11) was surprising as the intermediate amino-

nitrile (10, amino group *exo*) was expected based on the Strecker reaction of 2-norbornanone which yields the norbornane amino acid where the amino group is *exo* (confirmed by single crystal X-ray analysis).^[15] Clearly, formation of (11) must result from an intermediate amino-nitrile (9), where the amino group is *endo*. It is possible that both *endo* and *exo* are formed as an equilibrium mixture (Scheme 2) and that hydrogen bonding by the *endo* carboxylate stabilises the *endo* amino-nitrile.

Another possibility is that the *endo* face of the intermediate imine (8) is 'protected' by the neighbouring carboxylate [perhaps via equilibrium with the lactone (12)].

The Strecker reaction on the methyl ester (14) obtained from (7) by diazomethane esterification^[14a] was performed next. Once again the lactam (11) was formed in about 25% yield (based on amino-nitrile precursor) if performed as a one-pot reaction. It is possible that (14) was hydrolysed to (7) under the rather forcing conditions of the Strecker synthesis. Another possibility is that the amino group of the *endo* amino-nitrile (9) is in such close proximity to the carbonyl carbon of the *endo* carboxylate or ester moiety that nucleophilic attack occurs (with loss of water or methanol respectively) to give the lactam prior to the hydrolysis step. It was in fact possible to isolate the crude amino-nitrile (16) formed from the ester (14). The IR spectrum of this intermediate showed carbonyl absorptions at 1740 cm⁻¹ (unreacted ketone), 1720 cm⁻¹ (ester group of amino-nitrile) and 1700 cm⁻¹ (free acid carbonyl),^[17] but no vibrations at 1640 cm⁻¹ as would be expected for the lactam (11).^[17] This suggests that lactam formation occurs during the nitrile hydrolysis step. However, the result does indicate some hydrolysis of the ester group.

The Bucherer-Bergs reaction (sometimes referred to as the Bucherer-Lieb reaction),^[25, 26] was next considered in order to test if we would obtain the alternative isomer (amino group *exo*) via this route. The reaction was carried out on the ester (14) rather than the free acid (7). Under the conditions of the reaction the ester group was hydrolysed, the isolated product being the *spiro*-hydantoin (15). This *in situ* ester hydrolysis is somewhat surprising, but it has been observed in at least two other instances where a hydantoin ring was formed in close proximity to an ester group.^[27, 28] It was considered possible that the hydrolysis was assisted by the *endo* amino group, particularly since none of the other hydantoins in our series, where the ester group was distant to the hydantoin ring, showed any such hydrolysis.^[29]

Scheme 3

The formation of hydantoin (15) proceeded in high (88 %) yield. Attempts to hydrolyse (barium hydroxide followed by cold acidification)^[26] the hydantoin (15) to the glutamate analogue (2), again resulted in the formation of the lactam (11) in 92% yield giving an overall yield of (11) of approximately 80% based on keto-ester. Clearly, the Bucherer-Bergs procedure gives far better yields than the Strecker reaction in this case.

This indicated that the amino nitrile intermediate (16) (*i.e.* the precursor of the hydantoin) had an *endo* amino group as expected. This was confirmed by determining the X-ray crystal structure of the *spiro*-hydantoin (15).

An X-ray crystallographic analysis of hydantoin (15) reveals weak intramolecular hydrogen bonding between the *endo* carboxylate group and an *endo* ring hydrogen [O22...H3B-C3, 2.928(3) Å] (Fig. 2), as well as intermolecular hydrogen bonding. The molecules of (15) form centrosymmetric hydrogen-bonded R_2^2 (8) cyclic dimers through the carbonyl and the second amido group in the hydantoin ring [N62-H62...O63^a, 2.876(3) Å; $a = 1-x, 1-y, 1-z$] (Fig. 3). The carboxylic acid group does not give the usual cyclic hydrogen-bonded dimers^[20] but instead gives peripheral inter-dimer associations with one of the hydantoin carbonyl groups [O21-H21...O63^b, 2.724(2) Å; $b = 1-x, -y, 1-z$]. The second ring nitrogen is also linked to the other carboxyl oxygen extending the dimer into sheets [N64-H64...O22^c, 2.875(2) Å; $c = -x, -y, 1-z$] (Fig. 3).

Figure 2

Molecular configuration and atom numbering scheme for (15). Atoms are shown as 30% probability ellipsoids^[34]

Figure 3

Perspective view of the packing of (15) in the unit cell showing the hydrogen-bonding associations as broken lines.

This hydrogen bonding in hydantoin (15) is also evident in the IR spectrum which exhibits vibrations consistent with the literature at 3300 cm^{-1} and 3200 cm^{-1} (N-H stretches), 1770 cm^{-1} and 1725 cm^{-1} (carbonyls, hydantoin ring), 1690 cm^{-1} (carbonyl acid).^[21-24] The shift to lower frequency in the acid carbonyl is indicative of some intramolecular or intermolecular hydrogen bonding. This is also supported by the absence of broadness in the $3000 - 2600\text{ cm}^{-1}$ region of the spectrum.^[11]

The fact that for both the Strecker and Bucherer-Bergs methodologies the same (*endo*) amino group stereochemistry was obtained with both the acid (7) and ester (14) suggests that attack by cyanide on the imine (8) from the *endo* face is either sterically hindered by the carboxylate group and/or there is dipolar repulsion between the cyanide and carboxylate moieties in the transition state.

Interestingly, both (11) and (15) have recently been reported as precursors for compounds that inhibit leukocyte adhesion mediated by VLA4, however the yield was very low (18%) for (15), and not reported for (11). Only melting points were reported.^[30]

Conclusion

Cyanide-based amino acid synthesis, using either the Strecker or Bucherer-Bergs protocols with 6-norbornanone bearing a carboxylate or carbomethoxy group in the 2-*endo* position, leads to the tricyclic lactam (11). It would appear that the diastereoselectivity in these reactions is controlled by the presence of the *endo* carboxylate moiety.

Experimental

General

Melting points were performed on a digital Gallenkamp apparatus and are uncorrected. Solvents were distilled prior to use or were analytical grade. Infrared spectra were recorded on a JASCO IR-810 or on a Perkin-Elmer 1725 XFT-IR spectrometer. NMR spectra were recorded on a Varian 200 MHz spectrometer. ES-mass spectra were recorded on a Fisons VG Platform 8070 mass spectrometer. Thin layer chromatography was performed on silica gel plates (Merck, Kieselgel 60, F254, .255 mm). The spots were developed either by exposure to UV or Iodine. Acrylic acid and dicyclopentadiene were obtained from Aldrich and FLUKA respectively. Microanalysis was performed at the Microanalytical Service of the Chemistry Department of the University of Queensland.

(±)-Bicyclo [2.2.1] hept-5-ene-2-endo-carboxylic acid (5)

Freshly distilled cyclopentadiene (3) (33g) (0.5 mol) was added to acrylic acid (4) (30g) (0.4 mol). During addition the flask was cooled in an ice bath. When addition was complete the mixture was allowed to warm up to room temperature and stirred for 12 hr. Distillation (b.p. 99.5°C, 1.2 mm Hg, Lit. b.p.^[8] 139.0°C, 16 mmHg) gave a clear viscous oil of pungent odour (50g, 80%).

Mixture of *endo* (75%) and *exo* isomers (25%) (determined by ¹³C-NMR of methyl ester).

IR (NaCl disk, neat, oil): 3500-2400 (OH, acid), 1700 cm⁻¹ (C=O, acid).

¹H-NMR (CDCl₃): 11.93 (s), 6.11 (s), 3.51-1.16 ppm (series of multiplets).

¹³C-NMR: 182.96, 181.76, 138.08, 137.83, 135.72, 132.47, 49.71, 46.70, 46.39, 45.62, 43.36, 43.21, 42.57, 41.68, 30.32, 29.10 ppm.

(±)-5-exo-Bromo-6-endo-hydroxy-bicyclo[2.2.1]heptane-2-endo-carboxylic acid- γ-lactone (6).

Treatment of a solution of the unsaturated acid mixture (5) (1.0g, 7.24 mmol) in water (45 ml) containing sodium bicarbonate (3.0g, 35.7 mmol) with neat bromine (1.0 ml, 3.1g, 19.4 mmol) produced a light yellow oil which was extracted with ether (4 x 10 ml) after 16 hr reaction time. The extract was dried over MgSO₄, filtered, the ether removed *in vacuo* to yield a light yellow oil which crystallised on standing. Recrystallization from EtOAc.hexane gave clear white crystals of (6) (0.5g, 35%).

This procedure worked equally well on a large scale.

m.p. 64-66 °C (Lit. m.p.^[9] 64.8-65.9 °C)

IR (KBr disk): 1770 cm⁻¹ (C=O, lactone)

¹H-NMR (CDCl₃): 4.95 (1H, d, J=4.87Hz), 3.87 (1H, d, J=2.27Hz), 3.25 (1H, m), 2.60 (1H, br. s.), 2.68-2.55 (1H, m), 2.30-2.45 (1H, m), 2.55-2.05 (1H, m), 2.90-1.70 ppm (2H, m).

¹³C-NMR (CDCl₃): 179.19 (C=O, lactone), 87.80 (C-6), 53.59 (C-5), 46.03, 45.72 37.70, 35.90, 34.11 ppm (norbornane).

¹³C-DEPT: 87.80 (CH), 53.59 (CH), 46.03 (CH), 45.72 (CH), 37.70 (CH), 35.90 (CH₂), 34.11 (CH₂) ppm.

(±)-Bicyclo[2.2.1]hept-6-one-2-endo-carboxylic acid (7).

The bromo-lactone (6) (88g, 0.4 mol) was dissolved in MeOH (820 ml) and an ice-cold solution of KOH (67g, 1.2 mol) in dist. water (125 ml) was added in 5 portions with vigorous stirring. The mixture was then refluxed for 6 hr, allowed to cool and the MeOH removed *in vacuo*. The

aqueous residue was carefully neutralised with concentrated HCl, stirred at room temperature over Norit A charcoal (to remove a brown oil) filtered and acidified to pH 1. The acidified solution was extracted with Et₂O (4x200 ml), the extract dried over MgSO₄, filtered and the solvent removed *in vacuo* to yield a light yellow oil in which crystals formed upon standing. Recrystallization from DCM yielded a first crop. Two more crops were collected from reduced volumes. Colorless well formed crystals of (7) were obtained (29g, 45%). m.p. 102 - 104°C (Lit. m.p.^[10] 102-103°C)

IR (KBr disk): 3600 - 2400 (OH, acid), 1740 (C=O, ketone), 1700 cm⁻¹ (C=O, acid)

¹H-NMR (CDCl₃): 9.9 (1H, br. s., acid), 3.3 - 1.7 ppm (9H, m)

¹³C-NMR (CDCl₃): 216 (weak, br, C = O, ketone), 178.50 (C=O, acid), 53.42, 44.63, 42.83, 38.80, 35.38, 31.50 ppm (norbornane)

¹³C-DEPT: 53.42 (CH), 44.63 (CH₂), 42.83 (CH), 38.80 (CH₂), 35.38 (CH), 31.50 (CH₂) ppm.

Esterification with Diazomethane of (±) bicyclo[2.2.1]hept-6-one-2-endo-carboxylic acid (7) [14a].

The keto acid (7) (2.0g, 13mmol) was suspended in ether (10ml) and titrated with ethereal diazomethane until no more N₂ evolved upon addition of CH₂N₂ and a yellow colour persisted for 30 minutes. The ether was removed *in vacuo* to yield (14) as a yellow oil (2.1g, 96%) which required no further purification (compound was pure by TLC, ¹H-NMR and ¹³C-NMR).

IR (NaCl disk, oil, neat): 1740 cm⁻¹ (C=O ketone and ester), 1200 cm⁻¹ (C-O, ester)

¹H-NMR (CDCl₃, TMS): 3.67 (3H, ester), 2.95-3.15 (1H,m), 2.85 (1H,br.s.), 2.75 (1H, br.s.), 1.65-2.25 ppm (6H,m).

¹³C-NMR (CDCl₃, TMS): 214.65 (C=O, ketone), 173.88 (C=O, ester)

52.04 (CH₃, ester), 53.71, 44.61, 42.96, 38.90, 35.00, 31.00 ppm (norbornane)

¹³C-DEPT (CDCl₃): 53.71 (CH), 44.61 (CH₂), 42.96 (CH), 38.90 (CH₂), 35.00 (CH), 31.00 (CH₂) ppm.

(±)-6-endo-Amino-bicyclo[2.2.1]heptane-2-endo-carboxylic acid-γ-lactam-6-exo-carboxylic acid (11). [One-pot procedure]

To a reaction vial containing NH_4Cl (0.4 grams, 7.3 mmol) in conc. Ammonia solution (1.3 ml) and NaCN (0.4 gram, 7.3 mmol) in distilled water (0.6 ml), bicyclo[2.2.1]hept-6-one-2-endo-carboxylic acid (7) (1.0 gram, 6.5 mmol) was added dropwise at 0 °C. Upon completion of the addition the reaction vial was sealed, transferred to an oil-bath and heated with stirring at 50 °C (bath temp.) for 5 hr. The solution was allowed to cool and the volume reduced to approximately 1/3 of the original. Then conc. HCl (32%) (4 ml) was added and the mixture refluxed for 3 hr. Upon cooling in an ice-bath a white solid precipitated. This was filtered off, washed with ice cold water, ethanol and ether, and dried to give (11) as a white solid (0.3 g, 25%), identical by m.p., IR and ^1H -NMR to that obtained from the hydrolysis of (16).

(±)-6-endo-Amino-bicyclo[2.2.1]heptane-2-endo-carboxylic acid-γ-lactam-6-exo-carboxylic acid (9). [with isolation of amino-nitrile (16)]

The keto-ester (14) (5.9g, 35.3mmol) was dissolved in 50% aqueous methanol (30ml) in a pressure flask. To this a solution of KCN (3.6g, 56.1 mmol, 1.6 equiv.) and NH_4Cl (3.1g, 57.9mmol, 1.6 equiv.) in 50% aqueous methanol (30ml) was added. The flask was sealed and incubated in an oil bath at 80°C (bath temp.) with stirring for 8hr. The cooled mixture was transferred to a round-bottomed flask and the methanol removed *in vacuo*. The aqueous residue was extracted with ether (6 x 30ml), the ether extract dried over MgSO_4 , filtered and the solvent removed *in vacuo* to give crude (16) (2.3 g, 33%).

IR (NaCl disk, oil, neat): 3300 (N-H), 2220 (CN), 1740 ($\text{C}=\text{O}$, unreacted ketone), 1720 cm^{-1} ($\text{C}=\text{O}$, ester), 1700 cm^{-1} ($\text{C}=\text{O}$, free acid)

Hydrolysis of amino-nitrile (16)

The crude amino-nitrile (16), (2.3g, 11.9mmol, calculated as pure ester) was dissolved in 6M HCl (55ml, 27.6 equiv.), the solution placed in a pressure flask, sealed and incubated at 124 °C (bath temp.) for 12hr with stirring. The solution was cooled and the MeOH removed *in vacuo* and the aqueous residue acidified to pH 1 with conc. HCl to give, after drying, (11) as a white analytically pure solid (1.0 g, 46%). m.p. 302 - 305 °C dec. (Lit. m.p.^[30] 298-300 °C)

IR (KBr disk): 3600- 2400 (OH, acid), 3200 (N-H), 2980 (CH), 1720 cm^{-1} ($\text{C}=\text{O}$, acid), 1640 cm^{-1} ($\text{C}=\text{O}$, lactam). ^1H -NMR (d_6 -DMSO): 7.88 (1H, br. s.) 3.05-1.30 ppm (9H, m)

^{13}C -NMR (d_6 -DMSO): 180.14 ($\text{C}=\text{O}$, acid), 174.46 ($\text{C}=\text{O}$, lactam), 66.31 (C-6), 52.02, 42.58, 42.26, 37.75, 37.31, 33.60 ppm

^{13}C -DEPT: 52.02 (CH), 42.58 (CH_2), 42.26 (CH), 37.75 (CH), 37.3 (CH_2), 33.60 (CH_2) ppm.

ES - mass spec $M + 1$ 182, $M - 1$ 180

Anal. $\text{C}_9\text{H}_{11}\text{NO}_3$ requires C 59.6, H 6.1, N 7.7%, found: C 59.5, H 6.2, N 7.7%.

(±)-Bicyclo [2.2.1] heptane-2-endo-carboxylic acid-6-spiro-5'-hydantoin (15).

A solution of $(\text{NH}_4)_2\text{CO}_3$, (14g, 145.5 mmol, 4.1 equiv.) in 50 % aqueous EtOH (50ml) was placed into a 100 ml round-bottomed flask. A solution of the keto-ester (14) (5.8g, 35.0mmol) in 50 % aqueous EtOH (12ml) was added followed by a solution of KCN (4.7g, 72.30 mmol, 2.0 equiv.) in dist. water (12ml). The flask was fitted with a reflux condenser and kept at 60 °C (bath temp.) for 20hr with stirring. The mother liquor was reduced to 20 ml and acidified to pH 1 with conc. HCl and cooled in ice upon which an off-white solid precipitated which was filtered off by Buchner filtration.

One recrystallization from $\text{MeOH} \cdot \text{H}_2\text{O}$ 1:1 gave (15) (6.9 g, 88%) as colourless well-formed crystals suitable for X-ray analysis.

m.p. 296 - 298 °C dec. (Lit. m.p.^[30] 286 °C)

IR (KBr disk): 3300 (N-H), 3200 (N-H), 1770 (C=O, hydantoin), 1725 (C=O, hydantoin), 1690 cm^{-1} (C=O, acid)

^1H -NMR (d_6 -DMSO): 10.68 (1H, br. s., N-H), 6.90 (1H, br. s., N-H), 2.85-1.39 ppm (9H, m)

^{13}C -NMR (d_6 -DMSO): 179.55 (C=O, acid), 175.73 (C=O, amide), 157.32 (C=O, urea), 66.63 (C-6), 49.61, 44.96, 41.52, 39.38, 35.75, 28.73 ppm

^{13}C -DEPT: 49.61 (CH), 44.96 (CH), 41.52 (CH_2), 39.38 (CH_2), 35.75 (CH), 28.73 (CH_2) ppm

ES-mass spec: $M + 1$ 225, $M + \text{Na}$ 247, $M - 1$ 223

Anal. $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_4$ requires C 53.6, H 5.4, N 12.5%, Found: C 53.4, H 5.4, N 12.3%

Hydrolysis of spiro-hydantoin (15)

The spiro-hydantoin (15) (2.2g, 10.1mmol) was placed in a pressure flask and $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$ (8.0g, 25.4mmol, 2.5 equiv.) followed by dist. water (40ml) was added. The flask was sealed and the slurry kept at 124 °C (bath temp.) with stirring for 20hr. The excess $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$ was filtered off and the filtrate acidified to pH 1 with conc. HCl to give, after drying, (11) as an analytically pure solid (1.7g, 92%), identical by m.p., IR and ^1H -NMR to that obtained from the hydrolysis of (16).

Crystallography

Crystal Data. Compound (15) CCDC reference no. 211887. C₁₀H₁₂N₂O₄, *M_r* 224.22, triclinic space group *P*-1, *a* 6.732(2), *b* 8.266(3), *c* 9.481(2) Å, *F*(000) 236, *Z* 2, *D_c* 1.517 g cm⁻³, *μ*(Mo Kα) 1.19 cm⁻¹, temperature, 298(2) K. 4225 reflections measured [*2θ*_{max} 50°; *h*, 0 to 7; *k*, -9 to 9; *l*, -10 to 11], 1714 unique (*R*_{int} 0.071). Final *R*1 0.0315 (*F*); *wR*2 0.0805 (*F*²) [1293 observed with *I* > 2.0σ (*I*); *S* 0.89 (*F*²); Crystal size 0.10 by 0.10 by 0.08 mm.

X-ray diffraction data were collected at 298(2) K on an Enraf-Nonius CAD-4 diffractometer by using graphite crystal monochromatised Mo Kα X-radiation (*λ* = 0.71073 Å). Data were corrected for absorption using semi-empirical methods (psi scans)^[31]. The structure was solved by direct methods [SHELXS-86]^[32] and refined with anisotropic thermal parameters for all non-hydrogen atoms using SHELXL-93^[33]. General ring hydrogen atoms were included in the refinement at calculated positions as riding models while those involved in hydrogen-bonding interactions were located by difference methods and their positional and isotropic thermal parameters refined.

$$R_1 = (\sum |F_o| - |F_c|) / \sum |F_o| \text{ and } wR_2 = \{ \sum [w(F_o^2 - F_c^2)^2] / \sum [w(F_o^2)^2] \}^{1/2};$$

$$S = \{ \sum [w(F_o^2 - F_c^2)^2] / (n - p) \}^{1/2}$$

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