[1-β-Mercaptopropionic acid,2-(3,5-dibromo-L-tyrosine)]oxytocin, a Potent Inhibitor of Oxytocin†

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[1-β-Mercaptopropionic acid,2-(3,5-dibromo-L-tyrosine)]oxytocin was synthesized from a protected polypeptide intermediate that had been prepared by the condensation of *S*-ethylcarbamoyl-β-mercaptopropionyl-3,5-dibromotyrosine with H-Ile-Gln-Asn-Cys(Ec)-Pro-Leu-Gly-NH_2, using dicyclohexylcarbodiimide in dimethylformamide. The ethylcarbamoyl (Ec) protecting groups were removed by refluxing NH_3, and the resulting disulfhydryl peptide was oxidatively cyclized to the corresponding disulfide by ICH_2CH_2I. Purification of the analog was effected by partition chromatography and gel filtration. The analog possesses antioxytocic (pA_2 = 7.05) and antiavian vasodepressor (pA_2 = 7.44) activities but has neither agonist nor antagonist activity in the rat pressor assay.

Since the initial synthesis of oxytocin[2]

1 2 3 4 5 6 7 8 9
Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly-NH_2

there has been a continuing effort directed at elucidating the relationship between the gross structural features of the hormone and its pharmacological properties. In addition, there has been a concurrent interest in obtaining a detailed, three-dimensional structure of the hormone. Of the many analogs synthesized thus far, only [1-β-mercaptopropionic acid]oxytocin (deaminooxytocin),[3] [1-γ-mercaptobutyric acid]oxytocin,[3] [1,6-α-aminosuberic acid]oxytocin,[4] and [1-β-mercaptopropionic acid,4-α-aminobutyric acid]-oxytocin[5] have been obtained in crystalline form. In addition, the flavianic acid and *p*-hydroxyazobenzene-*p'*-sulfonic acid salts of oxytocin have been crystallized,[6,7] but none of these analogs or salts has been obtained in a form suitable for X-ray crystallographic analysis.

In an attempt to prepare a suitably crystalline analog, [1-β-mercaptopropionic acid,2-(3,5-dibromo-L-tyrosine)]-oxytocin ([1-β-Mpa,2-Dbt]oxytocin), an analog of deaminooxytocin in which the hydrogen atoms at the 3 and 5 positions of the aromatic ring of the tyrosine residue have been formally replaced by bromine atoms, has been synthesized. It was thought that the incorporation of bromine atoms into deaminooxytocin might produce a readily crystallizable analog and at the same time provide heavy atoms that would be useful in the structural analysis.

Interest in this analog stemmed also from a desire to learn more about the pharmacological effects of introducing substituents such as bromine into the amino acid residue at the 2 position of oxytocin. Analogs substituted with Tyr(OMe),[8,9] Tyr(OEt),[10] Phe(*p*-Me),[10] and Phe(*p*-Et)[10] residues in this position have been studied extensively and found, under conditions comparable to those employed in this study, to inhibit the action of oxytocin in a variety of assays including the oxytocic, avian vasodepressor, and rat pressor.[8-11] It was proposed that steric hindrance, rather than the absence of the hydroxyl group in the para position of the aromatic ring, is responsible for the inhibitory properties of these analogs.[10] Walter et al.[12] have suggested that the lipophilicity of the alkyl substituents may also play a role in the inhibition. The pharmacological testing of [1-β-Mpa,2-Dbt]oxytocin provided an opportunity to study the effects of lipophilic, bulky substituents on the tyrosine residue in an analog which retains the free phenolic function.

Preparation of [1-Mpa,2-Dbt]oxytocin involved the use of ethylcarbamoyl[13,14] (Ec) protection, which is removable by refluxing NH_3, for the sulfur atoms of cysteine and β-mercaptopropionic acid (β-Mpa). The more common *S*-benzyl protection was avoided because evidence suggests that its removal with Na in NH_3 would also involve loss of the halogen atoms from the aromatic ring.[9b] The required intermediate, β-Mpa(Ec)-Dbt-Ile-Gln-Asn-Cys(Ec)-Pro-Leu-Gly-NH_2, was prepared by condensation of β-Mpa(Ec)-Dbt-OH with H-Ile-Gln-Asn-Cys(Ec)-Pro-Leu-Gly-NH_2[14] by means of *N,N'*-dicyclohexylcarbodiimide in the presence of 1-hydroxybenzotriazole.[15] The *S*-ethylcarbamoyl groups were removed by refluxing NH_3, and the resulting disulfhydryl peptide was oxidized to the disulfide with diiodoethane.[16] The analog was purified by partition chromatography[17] and gel filtration.[18] Attempts to crystallize it from aqueous EtOH and aqueous HOAc have thus far been unsuccessful.

The highly purified [1-β-Mpa,2-Dbt]oxytocin was assayed (see Experimental Section) for oxytocic, avian vasodepressor (AVD), and rat pressor activities against the U.S.P. posterior pituitary standard. No measurable agonist activity was detected. The analog was found to be a potent inhibitor of both the oxytocic and AVD responses to synthetic oxytocin with pA_2 values of 7.05 ($\bar{M} = 8.9 \times 10^{-8}$, $\sigma = 2.0 \times 10^{-8}$) and 7.44 ($\bar{M} = 3.6 \times 10^{-8}$, $\sigma = 1.0 \times 10^{-8}$), respectively. No inhibition of the rat pressor response to synthetic 8-lysine-vasopressin was observed.

The antioxytocic and anti-AVD potencies of [1-β-Mpa,2-Dbt]oxytocin are roughly comparable to those of [1-L-penicillamine]oxytocin[19] (pA_2 = 6.86 and 7.50, respectively[20]), which was the first of a series of inhibitors containing two alkyl substituents in the 1 position of oxytocin that have been studied by du Vigneaud and coworkers. No precise comparison can be made with the antioxytocic or anti-AVD potencies of the *p*-alkyl- and *p*-alkoxyphenylalanine analogs previously discussed because of differences in assay conditions and methods of reporting the results. However, these analogs exhibit an antipressor activity not shown by [1-β-Mpa,2-Dbt]oxytocin.

While this work was in progress, [2-*o*-iodo-L-tyrosine]oxytocin, a closely related analog, was synthesized and found to be a potent inhibitor of the oxytocic response to oxytocin (pA_2 = 7.2) and also an inhibitor of the pressor response to pituitary extract.[21] The strong antioxytocic potencies of this halogen-containing analog and of [1-β-Mpa,2-Dbt]oxytocin demonstrate that with appropriately bulky and lipophilic substituents on the tyrosine residue it is not necessary to block or replace the phenolic functional group with alkyl substituents in order to produce an antioxytocic analog.

Experimental Section

Precoated plates of silica gel F-254 (0.25 mm, E. Merck) were used for thin-layer chromatography (TLC) in (A) $CHCl_3$–MeOH–HOAc (3:1:1) or (B) BuOH–HOAc–H_2O (3:1:1). Spots containing

†The symbols β-Mpa and Dbt are used to indicate β-mercaptopropionic acid and 3,5-dibromo-L-tyrosine, respectively. All other symbols follow the Recommendations (1971) of the IUPAC-IUB Commission on Biochemical Nomenclature.[1] All optically active amino acids are of the L configuration.

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5–20 μg were visualized by treatment with Cl_2 followed by KI–starch spray. Melting points were determined in open capillaries and are corrected. Optical rotations were measured on a Perkin-Elmer polarimeter Model 141. Where analyses are indicated only by the symbols for the elements, analytical results obtained were within ±0.4% of the theoretical values.

Pressor assays were carried out on anesthetized male rats.[22] Avian vasodepressor assays were performed on conscious chickens by the method of Coon,[23] as modified by Munsick et al.[24] Oxytocic assays were performed on uteri from rats in natural estrus according to the method of Holton,[25] as modified by Munsick[26] with the use of Mg-free van Dyke–Hastings solution as the bathing fluid.

The pA_2 values are defined by Schild[27] and are the negative logarithm to the base 10 of the average molar concentration ($\bar{M}$) of antagonist which will reduce the appropriate biological response to $2x$ units of pharmacologically active compound (agonist) to the response to x units of the agonist. The standard deviation in $\bar{M}$ is represented by σ. Specific details of the antioxytocic and anti-AVD assays are described by Vavrek et al.,[20] and the rat antipressor assay is described by Dyckes et al.[28]

β-Mpa(Ec)-OH. A solution of β-mercaptopropionic acid (10.6 g, 100 mmol) in dimethylformamide (DMF) (150 ml) was cooled to 0°, and freshly distilled ethyl isocyanate (9.68 g, 110 mmol) was added. The solution was warmed to room temperature over a 3-hr period and allowed to stand for 72 hr. The DMF was removed under reduced pressure to yield a clear, colorless oil which crystallized on standing. The product was recrystallized from 30 ml of benzene: 7.78 g (44%); mp 100–101° (lit.[29] mp 100.5°).

β-Mpa(Ec)-Dbt-OH·DCHA. β-Mpa(Ec)-OH (855 mg, 5.0 mmol) and *N*-methylmorpholine (NMM) (0.55 ml, 5.4 mmol) were dissolved in tetrahydrofuran (THF) (7 ml) and the solution was cooled to −10°. A solution of isobutyl chloroformate (0.65 ml, 5.0 mmol) in THF (3 ml) was added, and the mixture was stirred at −10° for 20 min. Dbt-OH·H_2O (2.14 g, 6.00 mmol) and NMM (1.68 ml, 15.0 mmol) in H_2O (6.5 ml) were added, and the solution was allowed to come to room temperature over a 90-min period. The solution was then acidified to pH 2 with concentrated HCl, and the THF was removed under reduced pressure. The resulting aqueous solution was extracted with 25 ml of EtOAc. The organic phase was extracted with 1 *N* HCl (2 × 25 ml) and saturated NaCl (2 × 25 ml) and dried over $MgSO_4$. This solution was evaporated to 10 ml under reduced pressure and dicyclohexylamine (DCHA) (0.93 ml, 4.73 mmol) was added. The resulting crystalline precipitate was collected and recrystallized from EtOH–EtOAc (10/50): 2.30 g (68%); pure by TLC (A, 0.78); mp 184–185° dec; $[\alpha]^{21}D$ +34.7° (*c* 1.00, 95% EtOH). Anal. ($C_{27}H_{41}Br_2N_3O_5S$) C, H, N, Br.

[1-β-Mpa,2-Dbt]oxytocin. The heptapeptide HBr·H-Ile-Gln-Asn-Cys(Ec)-Pro-Leu-Gly-NH_2[15] (284 mg, 0.317 mmol), NMM (0.081 ml, 0.794 mmol), 1-hydroxybenzotriazole[16] (76.8 mg, 0.569 mmol), and the dipeptide β-Mpa(Ec)-Dbt-OH (189 mg, 0.380 mmol), freed from the DCHA salt by partitioning between EtOAc and 1 *N* H_2SO_4, were dissolved in DMF (8 ml). The solution was cooled to 0° and *N,N'*-dicyclohexylcarbodiimide (77.0 mg, 0.380 mmol) was added. The solution was stirred at 0° for 1 hr and then at room temperature for 17 hr. The products were precipitated by the addition of EtOAc (25 ml) and isolated by centrifugation. The material was washed at the centrifuge with EtOAc (3 × 25 ml), 95% EtOH (3 × 25 ml), and Et_2O (3 × 25 ml) and dried in vacuo: 338 mg (83%); mp 240–243°; $[\alpha]^{21}D$ −32.5° (*c* 0.23, DMF); TLC (A) showed a trace of a slow-moving contaminant. This product was used successfully for the preparation of the analog.

A solution of this protected peptide (177 mg, 137 μmol) in NH_3 (150 ml, freshly distilled from Na) was held at reflux for 4 hr. The solution was evaporated to a small volume and lyophilized. The resulting white powder was dissolved in 500 ml of water–acetone (1:1) and oxidized with 57.5 mg (205 μmol) of ICH_2CH_2I.[16] After 10 min the Ellman test[30] for free sulfhydryl was negative. The solution was concentrated in vacuo and lyophilized. The residue was subjected to partition chromatography[17] on Sephadex G-25 (100–200 mesh) in *n*-BuOH–C_6H_6–pyridine–HOAc–H_2O (500:500:15:35:950) at a flow rate of 21 ml/hr. A single major peak emerged at R_f 0.68 (as determined by the Folin–Lowry method[31]). The fractions comprising the peak were pooled and lyophilized to yield 101 mg (64.3%) of partially purified product. The material was further purified by gel filtration[18] on Sephadex G-25 in 20% HOAc. A single peak emerged at 85% of the column volume and yielded 86 mg (86% recovery). To remove any traces of Sephadex dissolved by the 20% HOAc; this product (24.6 mg) was subjected to gel filtration in 0.2 *N* HOAc. A single peak emerged at 119% of the column volume and yielded 21.8 mg (88.7% recovery): TLC (B) 0.55; $[\alpha]^{21}D$ −86.2° (*c* 0.17, 1 *N* HOAc). Anal. ($C_{43}H_{63}Br_2N_{11}O_{12}S_2 \cdot 3H_2O$) C, H, N, Br. Amino acid analysis[32] of a sample hydrolyzed in 6 *N* HCl at 110° for 24 hr was performed on a Beckman Model 116 analyzer using a single column system.[33] Dibromotyrosine emerged between Lys and NH_3. The following molar ratios were obtained: Asp, 0.98; Glu, 1.00; Pro, 0.99; Gly, 0.92; ½Cys, 0.48; mixed disulfide of Cys and β-Mpa, 0.50; Ile, 1.01; Leu, 1.05; Dbt, 1.08; NH_3, 2.97.

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Book Reviews

Investigation of Rates and Mechanisms of Reactions. Third Edition. Part I. General Considerations and Reactions at Conventional Rates. Edited by E. S. Lewis. (Volume VI in the series, "Techniques of Chemistry". Edited by A. Weissberger.) Wiley, New York, N.Y. 1974. xiii + 838 pp. 22.5 × 15 cm. $42.50.

This volume is the successor to Part I of Volume VIII of the highly respected Weissberger series, "Technique of Organic Chemistry". This new series has combined the former with "Technique of Inorganic Chemistry" in recognition of the artificiality inherent in division of methodology by subfields. It is the stated aim of the Editor to avoid thorough reviews of applications of the various techniques but rather to concentrate on a few illustrative examples. There is also the expressed desire to make individual chapters more readable and concise. In the opinion of this reviewer, the Editor has succeeded admirably in reaching these aims.

The coverage within the 14 chapters ranges from detailed discussions of experimental techniques to considerations of abstruse theoretical ideas. Since 17 contributing authors are involved, considerable variation in the nature of the coverage of each topic must be expected. Some chapters are all too brief; others are quite comprehensive. Almost all share a uniformly high quality, which was the trademark of the original Weissberger Series.

Chapter I, "General Methods of Rate and Mechanism Study" (E. S. Lewis) consists of introductory material, much of which is at the level of a good undergraduate organic text.

Chapter II, "Activated-Complex Theory: Current Status, Extensions, and Applications" (R. A. Marcus) develops the underlying theory.

Chapter III, "Homogeneous Gas-Phase Reactions" (A. Maccoll) describes apparatus, including both static and flow systems, detection methods, analysis of results, and assignments of mechanism. This thorough treatment is complemented by numerous examples and tabulations.

Chapter IV, "Kinetics in Solution" (J. F. Bunnett) repeats some introductory material en route to the development of various rate equations. There follow a cursory coverage of the requisite apparatus, a brief review of available techniques, a discussion of precision and errors, and an extensive discussion of the pitfalls awaiting the unwary.

Chapter V, "Kinetic Isotope Effects" (W. H. Saunders, Jr.) discusses the theory of both primary and secondary isotope effects, illustrated with a number of examples for both deuterium and tritium, delves into solvent isotope effects, and concludes with a consideration of heavier elements.

Chapter VI, "Tracer Methods" (V. F. Raaen) briefly considers analytical applications followed by a discussion of several examples of applications to mechanistic studies of rearrangements and ion-pair return. There follows some practical information dealing with purchase and preparation of labeled compounds, including a brief survey of more commonly used nucleides, both stable and radioactive.

Chapter VII, "Stereochemistry and Reaction Mechanism" (R. V. Stevens, W. E. Billups, and B. Jacobson) considers nucleophilic and electrophilic ionic aliphatic substitution, olefin-forming elimination, and electrophilic addition to double bonds and concludes with a lengthy discussion of various reactions subject to orbital symmetry control.

Chapter VIII, "From Kinetic Data to Reaction Mechanism" (J. F. Bunnett) covers the effects of medium, temperature, pressure, and acidity on reaction rates and discusses some of the principles and criteria for determination of reaction mechanisms.

Chapter IX, "Kinetics of Complex Reactions" (R. M. Noyes) discusses consecutive and competitive processes, illustrated with a number of representative examples.

Chapter X, "Homogeneous Inorganic Reactions" (J. H. Espenson) deals with applications peculiar to inorganic and organometallic processes.

Chapter XI, "Homogeneous-Solution Catalysis by Small Molecules and by Enzymes" (M. F. Dunn and S. A. Bernhard) covers catalyst complexes and kinetics pertaining thereto, enzyme kinetics, transients, and intermediates and discusses examples of catalytic mechanisms in protic solvents.

Chapter XII, "Mechanism in Heterogeneous Catalysis" (M. Boudart and R. L. Burwell, Jr.) considers kinetics of heterogeneous catalytic reactions, isotopic tracers, poisoning, applications of stereochemical data and of infrared absorption spectroscopy, spectroscopy of catalysts during reactions, adsorption studies, and correlations among catalytic properties, activity, and selectivity.

Chapter XIII, "Use of Computors" (K. B. Wiberg) considers data processing and data collection for simple and also for complex reactions. Several sample programs are included.

Chapter XIV, "Linear-Free Energy Relations" (R. Fuchs and E. S. Lewis) examines the nature and basis of linear free-energy relations in general and of the Hammett equation in particular, as well as their failure. Experimental planning and data treatment are also discussed.

One of the most delightful pieces of scientific writing which this reviewer has seen may be found in Chapter VIII. The discussion of the determination of reaction mechanisms, including suitable references to Sherlock Holmes, should be required reading for all undergraduate and graduate students, as well as all practicing chemists who may ever be tempted to assign a mechanism to a reaction.

Only a few items appear on the negative side. There is a dearth of cross references between chapters, which results in some duplication, particularly of introductory material, although such duplication allows each chapter to stand by itself. In Chapter VII the terminology for reaction classification (e.g., E1cB) is not well defined and the consequences of radical intermediacy upon stereochemistry are not discussed. Instead, an excessively long section of this chapter is devoted to "Orbital Symmetry and Electrocyclic Reactions (it should be "Pericyclic") in a manner which is too obscure for the novice but oversimplified for the specialist. Better coverages of this topic are available. A potentially more serious problem is the fact that three references, sought out by this reviewer in other chapters, were found to be in error or missing.

Most chapters include a large number of references, and there are some as recent as 1974. This constitutes a tribute, to both editor and publisher, for the production of a multi-author volume without delay. As befits the topics covered, there are many older references. Each chapter includes a separate, detailed table of contents and there is a general index. In addition to providing the necessary background for mechanistic investigation, this book is also an excellent reference source. It is highly recommended, not only for libraries but for all chemists to whom determination or interpretation of reaction mechanisms is of interest. Considering current book prices, its cost is reasonable.

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Synthetic Fibrinolytic Thrombolytic Agents. Chemical, Biochemical, Pharmacological, and Clinical Aspects. Edited by K. N. von Kaulla and J. F. Davidson. Charles C Thomas, Springfield, Ill. 1975. 489 pp. 25 × 16.5 cm. $34.50.

Mortality from thrombogenic vascular disorders is nearly three times that caused by cancer. Treatment with anticoagulants and thrombolytic enzymes may be useful but is severely limited. Anti-