Synthesis of Desamino-desoxy-oxytocin, a Biologically Active Analogue of Oxytocin*

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In the study of the relationship between structure and biological activity in the neurohypophysial hormones, oxytocin and vasopressin, attention has recently been focused in this and other laboratories on the chemical functional groups. Aside from peptide linkages, these chemical functional groups in oxytocin consist of a primary amino, a phenolic hydroxyl, three carbamate groups, and a disulfide linkage. The importance of the phenolic hydroxyl group and the primary amino group to the biological activity of oxytocin has already been investigated through the preparation and study of various derivatives of oxytocin in which one of these functional groups is blocked by a substituent and through the synthesis and study of two analogues of the hormone, one lacking the phenolic group (desoxy-oxytocin) (1-4) and the other lacking the amino group (desamino-oxytocin) (5, 6).

Desoxy-oxytocin (2-phenylalanine-oxytocin) possesses approximately one-sixteenth of the oxytocic activity of oxytocin and approximately one-eighth of its avian depressor activity (1, 2). When the oxytocic activity is determined on the cat uterus in situ, the desoxy analogue is approximately one-third as active as oxytocin (2). The rat pressor activity of desoxy-oxytocin is approximately one-tenth that of oxytocin and the antidiuretic activity is also very low (3, 4). It may be concluded from these data that the phenolic hydroxyl group in oxytocin is not essential for the production of the biological responses characteristic of oxytocin, but the presence of the phenolic group greatly enhances these activities. Although desoxy-oxytocin is less active than oxytocin, it is a highly potent pharmacological agent with respect to certain activities of the hormone when one considers the amount of compound necessary to produce an effect.

On the other hand, the blocking of the phenolic hydroxyl group of oxytocin by a methyl group through total synthesis of O-methyl-oxytocin from O-methyltyrosine (7, 8) leads to an analogue which possesses approximately one-tenth of the avian depressor activity exhibited by desoxy-oxytocin (7). Furthermore, the O-methyl-oxytocin has some inhibitory effect on the pressor response of arginine-vasopressin (7) and a marked inhibitory effect on the oxytocic response of oxytocin on the isolated rat uterus (8, 9). Thus the effects of blocking the phenolic hydroxy group of oxytocin with a methyl group differ considerably from those of eliminating the group entirely. This divergence in results, depending upon whether the functional group has been eliminated entirely or blocked with a substituent, may have a wider significance than its application to the study of oxytocin and must be borne in mind in the making of deductions from the results of studies in which the blocking technique is employed to determine the significance of functional groups to the activities of various hormones and enzymes.

Desamino-oxytocin (1-β-mercaptoheptanoyl acid oxytocin) (5, 6), which lacks the primary amino group, possesses very high avian depressor and oxytocic activities in comparison with oxytocin and exhibits an antidiuretic activity approximately 5 times that of oxytocin (8).1 Its rat pressor activity is approximately one-third that of oxytocin. Thus the amino group in oxytocin is not necessary for the manifestation of these biological activities.

In contrast to the effect of replacing the amino group of oxytocin with a hydrogen, as in desamino-oxytocin, the attachment of a glycyl radical to the amino group, as in glycyl-oxytocin (10), results in a derivative that shows a marked inhibitory effect on the avian depressor activity of oxytocin. Furthermore, in early work in this laboratory Cash and Studer2 found that treatment of oxytocin with acetic anhydride produced a product which was devoid of avian depressor activity and to some extent inhibited this activity of oxytocin, and Boissonnas et al. (4) have recently reported an inhibitory effect of N-acetyl-oxytocin on the avian depressor activity of oxytocin.

It is the purpose of the present paper to describe the synthesis and biological properties of an analogue of oxytocin lacking both the free amino and phenolic hydroxyl groups. In this desamino-desoxy-oxytocin (Fig. 1) the half-cystine residue in the 1-position of oxytocin is replaced by a β-mercaptoheptanoyl acid residue and the tyrosine residue in the 2-position is replaced by a phenylalanine residue.

The synthesis of desamino-desoxy-oxytocin was carried out by use of the stepwise p-nitrophenyl ester procedure employed earlier for the synthesis of oxytocin by Bodanszky and du Vigneaud (11). The protected heptapeptide, carbobenzoxy-L-isoleucyl-L-glutamyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-L-leucylglycinamide (11), was treated with hydrobromide in glacial acetic acid to remove the carbobenzoxy group. An aqueous solution of the heptapeptide hydrobromide was then treated with an anion exchange resin in the OH− form, and the free heptapeptide was crystallized from water. This crystalline heptapeptide was analytically pure and possessed a sharp melting  

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1 A more detailed study of the pharmacological effects of oxytocin and desamino-oxytocin has recently been made (Chan and du Vigneaud, Endocrinology, in press).

2 W. D. Cash and R. O. Studer, unpublished observations.
point which was not substantially raised by recrystallization. The amino acid analysis of a hydrolysate of the heptapeptide revealed the presence of the seven amino acids and ammonia in the expected molar proportions. This compound was obtained in amorphous form by Jošt, Rudinger, and Šorm (8) after purification by countercurrent distribution.

The crystalline heptapeptide was coupled with p-nitrophenyl carbobenzoxy-L-phenylalaninate in dimethylformamide to give the protected octapeptide, from which the carbobenzoxy group was removed to obtain the free octapeptide. The latter compound was coupled with p-nitrophenyl S-benzyl-$\beta$-mercaptopropionate (5, 6) in dimethylformamide to give S,S'-dibenzyldesamino-desoxy-oxytocine (8) (S-benzyl-$\beta$-mercapto-L-prolyl-$\beta$-asparaginyl-L-lysylglycylglycinamide) as an amorphous solid. This substance was also prepared in somewhat lower yield by the stepwise p-nitrophenyl ester procedure without isolation of the free heptapeptide and octapeptide.

For the preparation of desamino-desoxy-oxytocin the S,S'-dibenzyldesamino-desoxy-oxytocine was treated with sodium in liquid ammonia and the reduced material thus obtained was then oxidized, after evaporation of the ammonia, by potassium ferricyanide in aqueous solution at pH 6.5 to 7.0. The preliminary experiments on the oxidation of desamino desoxy oxytocine with the use of potassium ferricyanide were carried out before the use of ferricyanide for the preparative scale synthesis of desamino-oxytocin (6). The solution of desamino-desoxy-oxytocin from the oxidation step was assayed for avian depressor activity and, after evaporation of the solvent, was distributed for 200 transfers in an all-glass countercurrent distribution machine in the system butanol-toluene-0.05% acetic acid (3:2:5) used previously in the purification of desamino-oxytocin. The biologically active material was concentrated in a single peak having a partition coefficient (K) of 2.5. Desamino-oxytocin has a K of 0.5 in this solvent system. The value for the desamino-desoxy analogue reflects the higher solubility of this peptide in the phase richer in organic solvent, due in all probability to the absence of the phenolic hydroxyl group as well as the dibenzyl group. The desamino-oxytocine so obtained gave the expected amino acid and elemental analyses and possessed an optical rotation of $[\alpha]_D^{25} = -107^\circ$ (c, 0.5 in acetic acid), compared with a value of $-107^\circ$ for desamino-oxytocin (6).

This desamino-desoxy analogue of oxytocin was assayed against the U.S.P. Posterior Pituitary Reference Standard (12) for avian depressor activity according to the procedure of Munsick, Sawyer, and van Dyke (13) and for oxytocic activity according to the method of Holton (14) as modified by Munsick (15) with the use of magnesium-free van Dyke-Hastings solution. It was also tested for pressor activity in urethane-anesthetized rats according to the method described in the United States Pharmacopeia (16) and for antiuretic activity in rats according to the method of Jeffers, Livezey, and Austin (17) as modified by Sawyer (18). The desamino desoxy oxytocin was found to possess approximately 60 units of avian depressor activity and 25 units of oxytocic activity, as well as small amounts of pressor and antiuretic activities. The potencies of this compound are compared with those of oxytocin, desamino-oxytocin, and desoxy-oxytocin in Table I.

It is obvious that the primary amino and phenolic hydroxyl groups of oxytocin can both be replaced by hydrogen atoms with retention of an appreciable amount of oxytocic and avian depressor activities. Moreover, these activities are almost the same in both desamino-desoxy-oxytocin and desoxy-oxytocin. With regard to the pressor effect there is a progressive fall in the potency of oxytocin upon loss of the amino group, the phenolic group, and finally of both of these groups. On the other hand, the antiuretic activity of desamino-desoxy-oxytocin is of the same order as that of the desoxy analogue. Finally, these results on desamino-desoxy-oxytocin demonstrate that the biological effects of oxytocin discussed herein may be present qualitatively in the absence of both the primary amino and the phenolic hydroxyl group. These facts are undoubtedly pertinent.

Table I

<table>
<thead>
<tr>
<th>Activity</th>
<th>Oxytocin$^a$</th>
<th>Desamino-oxytocin$^b$</th>
<th>Desoxy-oxytocin</th>
<th>Desamino-desoxy-oxytocin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avian depressor (fowl) .</td>
<td>507 ± 23</td>
<td>733 ± 23</td>
<td>60 ± 2</td>
<td>61 ± 2</td>
</tr>
<tr>
<td>Oxytocic (rat uterus) .</td>
<td>488 ± 5</td>
<td>684 ± 32$^c$</td>
<td>30 ± 22$^d$</td>
<td>~25</td>
</tr>
<tr>
<td>Pressor (rat) .</td>
<td>3.1 ± 0.1</td>
<td>1.1 ± 0.1</td>
<td>~0.4$^d$</td>
<td>~0.04</td>
</tr>
<tr>
<td>Antiuretic (rat) .</td>
<td>2.1 ± 0.2</td>
<td>1.0 ± 2</td>
<td>~0.3$^a$</td>
<td>~0.30</td>
</tr>
</tbody>
</table>

$^a$ These values were recently obtained in this laboratory for a highly purified sample of synthetic oxytocin (see Footnote 1).

$^b$ See (6) and Footnote 1.

$^c$ See (1).

$^d$ See (2-4).

$^e$ This value is the mean of values obtained upon assays on uteri of rats at various estrous stages. The effect of the estrous cycle on the oxytocic response of desamino-oxytocin with respect to that of oxytocin will be the subject of a forthcoming presentation (Chan, O'Connell, and Pomeroy, manuscript in preparation).
to the formulation of any hypothesis regarding the mechanism of action of oxytocin at the molecular level.

**Experimental Procedure**

1. **Isocysteinyl-γ-glutaminy1-γ-asparaginyl-S-benzyl-γ-glutaminy1-γ-prolyl-γ-leucylglycinamide** — Carbobenzyoxyl-γ-glutaminy1-γ-asparaginyl-S-benzyl-γ-cysteinyl-γ-prolyl-γ-leucylglycinamide (11), 16.0 g, was suspended in 50 ml of dry glacial acetic acid. Hydrogen bromide in glacial acetic acid (40% weight per weight, 50 ml) was added and the mixture was kept at room temperature for 1½ hours. The solution was poured with stirring into 600 ml of dry, peroxide-free ether. The solid hydrobromide was allowed to settle, separated, and washed twice by decantation with 400-ml portions of ether. The ether was then removed from the solid by evaporation in a vacuum, and the residue was dissolved in 150 ml of dry methanol. The solution was passed through a column (4.5 x 15 cm) of IRA-410 in the OH⁻ form. The resin was washed with two 150-ml portions of hot methanol. The eluates were combined and evaporated to dryness. Boiling water, 50 ml, was passed through a 2.4 x 30 cm column of IRA-410 in the OH⁻ form. The column was washed with 150 ml of water, and the eluates were evaporated to dryness. Glacial acetic acid, 50 ml, was added. The solid was dissolved in 40 ml of dimethylformamide and treated with 1 ml of triethylamine at 60°. p-Nitrophenyl S-benzyl-γ-mercaptopropionate, 0.5 g, was dissolved in 15 ml of warm, dry glacial acetic acid. Hydrogen bromide in glacial acetic acid (25% weight per weight, 40 ml) was added. The mixture was allowed to stand at room temperature for 33 hours. The mixture was cooled and 1.8 g of p-nitrophenyl carbobenzyoxyl-γ-phenylalanyl-γ-isoleucyl-γ-glutaminyl-γ-asparaginyl-γ-benzyl-γ-cysteinyl-γ-prolyl-γ-leucylglycinamide was added. The reaction was allowed to proceed for 4 days at room temperature. Ethyl acetate, 400 ml, was added to the mixture, and after being shaken vigorously, the suspension was filtered. The solid material was washed with 150 ml of ethyl acetate in small portions and the product was dried at 100° in a vacuum for 8 hours; wt. 4.0 g, m.p. 244-245°, [α]⁺ = -40.8° (c, 1 in dimethylformamide), lit. (1) m.p. 251-253°, [α]⁺ = -41° (c, 1 in dimethylformamide). The carbobenzyoxyl-p-phenylalanyl-γ-isocysteinyl-γ-glutaminy1-γ-asparaginyl-S-benzyl-γ-cysteinyl-γ-prolyl-γ-leucylglycinamide—The free heptapeptide, 3 g, was dissolved in 40 ml of dimethylformamide at 60°. The solution was cooled and 1.8 g of p-nitrophenyl carbobenzyoxyl-p-phenylalanine were added. The reaction was allowed to proceed for 4 days at room temperature. Ethyl acetate, 400 ml, was added to the mixture, and after being shaken vigorously, the suspension was filtered. The solid material was washed with 150 ml of ethyl acetate in small portions and the product was dried at 100° in a vacuum for 8 hours; wt. 4.0 g, m.p. 244-245°, [α]⁺ = -40.8° (c, 1 in dimethylformamide), lit. (1) m.p. 251-253°, [α]⁺ = -41° (c, 1 in dimethylformamide).

The protected heptapeptide, 6.5 g, was finely powdered and suspended in 40 ml of dry glacial acetic acid. Hydrogen bromide in glacial acetic acid (40% weight per weight, 25 ml) was added. The mixture was allowed to stand at room temperature for 1 day, and an equal volume of ethyl acetate was added. The solution was poured with stirring into 400 ml of dry, peroxide-free ether. The hydrobromide was collected by centrifugation of the suspension. The solid material was washed with 300 ml of ether and separated by centrifugation. Residual ether was removed from the solid by evaporation in a vacuum. The residue was dissolved in 400 ml of dry methanol, and the solution was passed through a column of IRA-410 in the OH⁻ form which had been washed with 200 ml of warm methanol. The eluate and washings were combined and concentrated to a volume of 50 ml. The white solid which had separated was collected, washed with methanol, and dried in a vacuum at 100° for 10 hours; wt. 4.0 g, m.p. 215-217°, [α]⁺ = -41° (c, 1 in dimethylformamide).

The heptapeptide, 0.5 g, was recrystallized in the form of needles from 10 ml of boiling water; wt. 0.42 g, m.p. 211-212°. The heptapeptide, 0.5 g, was recrystallized in the form of needles from 10 ml of boiling water; wt. 0.42 g, m.p. 211-212°.

A sample was hydrolyzed in 6 N HCl at 110° for 17 hours and analyzed on the amino acid analyzer. The following molar ratios were obtained with the value for isoleucine taken as 1: leucine, 1.0; S-benzylcysteine, 1.1; isoleucine, 1.0; proline, 1.1; glutamic acid, 1.0; aspartic acid, 1.0; glycine, 1.1; and ammonia, 2.9.

S-Benzyl-β-mercaptopyropinyl-γ-phenylalanyl-γ-isocysteinyl-γ-glutaminy1-γ-asparaginyl-S-benzyl-γ-cysteinyl-γ-prolyl-γ-leucylglycinamide (S,S'-Dibenzyl-desamino-desoxy-oxytocine)—Finely powdered carbobenzyoxyl-p-phenylalanyl-p-isocysteinyl-γ-prolyl-γ-leucylglycinamide (1.0 g), prepared throughout by the method of Bodanszky and du Vigneaud (1), was dissolved in 15 ml of warm, dry glacial acetic acid. Hydrogen bromide in glacial acetic acid (25% weight per weight, 25 ml) was added and the mixture was allowed to stand at room temperature for 3½ hours. The mixture was evaporated in a vacuum (water pump). The residue was taken up in 3 ml of methanol and 20 ml of ether were added. The crystalline, hygroscopic hydrobromide was collected by filtration, washed with ether, and dried in a vacuum for 10 hours over KOH pellets and CaCl₂. The dry material was dissolved in 10 ml of dimethylformamide and treated with 1 ml of triethylamine at 0°. p-Nitrophenyl S-benzyl-β-mercaptopyroproline, 0.5 g, was

4 All melting points were taken in capillaries and are corrected. Substances melting above 150° were placed in the bath 10-15° below the melting point, and the rate of heating was approximately 2° per minute.
added to the reaction mixture. After 3 days at room temperature, 100 ml of ethyl acetate were added. The solid was collected, washed with ethyl acetate and ethanol, and dried in a vacuum at 100° for 4 hours; wt. 0.86 g, m.p. 252-253°, [a]D 20 +44.3° (c, 0.5 in dimethylformamide).

In a synthesis of this S,S'-dibenzyl-desamino-desoxy-oxytocine employing the free octapeptide, prepared in turn from the crystalline heptapeptide, 2.8 g of l-phenylalanine-l-isoleucyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-L-leucylglycinamide were dissolved in 60 ml of dimethylformamide at 50°. The solution was cooled and 2 g of p-nitrophenyl S-benzyl-β-mercaptopyrroprionate were added. The mixture was allowed to stand at room temperature for 4 days. The amount of solid material was found to increase in amount each day. Ethyl acetate, 300 ml, was added with shaking to the comioild mass. The solid was collected, washed 6 times with 50-ml portions of ethyl acetate (300 ml), and dried in a vacuum at 100° over P2O5 for 4 hours; wt. 3.2 g, m.p. 251-252°, [a]D -45.4° (c, 1 in dimethylformamide).

**Preliminary Experiments with Potassium Ferricyanide as Oxidant for Conversion of Dithiol, Desamino-desoxy-oxytocine, to Cyclic Disulfide**—These experiments were carried out to determine whether and under what conditions potassium ferricyanide could be used in place of oxygen for conversion of dithiols related to oxytocine to the corresponding cyclic disulfides. Aeration was used for this purpose in the original synthesis of oxytocine. Difficulty had been encountered with the use of aeration in the preparation of desamino-oxytocine (5, 6) presumably due to the lack of the amino group. Since it is known that phenols can be oxidized under certain conditions by potassium ferricyanide, preliminary experiments were carried out with desamino-desoxy-oxytocine, which lacks the phenolic hydroxyl group, in order to determine whether ring closure would take place. For these experiments S,S'-dibenzyl-desamino-desoxy-oxytocine, 115.5 mg, was dissolved in 100 ml of liquid ammonia freshly distilled from sodium. The protected peptide was treated with sodium until a faint blue color persisted in the solution. Most of the ammonia was evaporated in a stream of dry nitrogen and the final 10 ml were removed by lyophilization. The residue was dissolved in 110 ml of 0.05% acetic acid. The pH values of five 20-ml aliquots of this solution were adjusted to 5.5, 6, 6.5, 7, and 7.5, respectively, and the solutions were then titrated with 0.0455 N potassium ferricyanide solution. The appearance of a yellow color in the solution indicated that the end point had been reached. Estimation of the avian depressor activity of the solutions before and after oxidation showed that no loss in biological activity had occurred during the oxidation, and in most cases an increase in avian depressor activity was observed. Passage of the solution through a 0.9 × 2.5-cm column of ion-exchange resin (AG 3-X4, 200 to 400 mesh in chloride form) was found to be a convenient way of removing both ferrocyanide and excess ferricyanide ions from the solution without loss of biological activity.

**1-β-Mercaptopyrpyroprionic acid β-phenylalanine-oxytocin (Desamino-desoxy-oxytocine)**—A solution of 342 mg of S-benzyl-β-mercaptopyrpyroprionic-L-phenylalanine-L-isoleucyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-L-leucylglycinamide in 500 ml of boiling liquid ammonia, freshly distilled from sodium, was treated with 24 mg of sodium until a blue color persisted for 2 minutes. Glacial acetic acid, 1.0 ml, was added, and most of the ammonia was removed by passage of a stream of dry nitrogen through the solution until the volume was approximately 15 ml. The remaining ammonia was removed by lyophilization in a vacuum (water pump). The residue was dissolved in a mixture of 100 ml of propanol and 235 ml of water. A clear solution, pH 6.65, was obtained and assay of this solution for avian depressor activity showed a total of 4580 units. The 1-β-mercaptopropionic acid-2-phenylalanine-oxytocine was oxidized by titration with 0.011 N potassium ferricyanide solution; 33 ml were required to impart a yellow color to the solution and an excess of 5 ml was then added. The solution was deionized by passage through two columns of ion exchange resins: the first column, 2.4 × 10 cm, contained Dowex 50W-X12 in the H+ form, 100 to 200 mesh. The acidic eluate and washings, 50 ml, were then passed through a 2.4 × 5-cm column of AG 3-X4, 100 to 200 mesh, in the OH- form. The column was washed with 50 ml of water. Assay of the combined eluate and washings for avian depressor activity showed a total of 5600 units. The solution was evaporated in a flash evaporator to a volume of approximately 25 ml. For further purification this solution was placed in the first five tubes of a 200-tube countercurrent distribution apparatus. The peptides were distributed in a butanol-toluene-0.05% acetic acid solvent system (6). After 200 transfers, a peak containing material with a partition coefficient (K) of approximately 2.5 emerged. Avian depressor activity was present in tubes No. 130 to 155 and the peak occurred at tube No. 140. The theoretical curve calculated for the K value 2.5 was in excellent agreement both with the curve obtained by plotting the weight determinations (20) and with those obtained by means of the avian depressor assay values and the Folin-Lowry color values (21). The contents of tubes No. 130 to 152 were pooled, evaporated in a flash evaporator to a volume of approximately 60 ml, and lyophilized; wt. 90.5 mg, [a]D 20 -103° (c, 0.5 in N acetic acid).

A sample was hydrolyzed in 6 N HCl at 110° for 17 hours and analyzed in the Beckman-Spinco amino acid analyzer with a delay of 1 hour in the time at which the buffer was changed as described previously for the analysis of desamino-oxytocine. The following molar ratios were obtained, with the value for leucine taken as 1: leucine, 1.0; isoleucine, 0.9; phenylalanine, 0.9; proline, 1.0; glutamic acid, 1.0; aspartic acid, 1.0; glycine, 1.0; and ammonia, 2.9. In addition, cystine (0.23) and the mixed disulfide of L-cysteine and β-mercaptopyrpyroprionic acid (0.5) were present. These two sulfur compounds thus account for the half-cystine residue in the analogue (see [6]).

**SUMMARY**

The importance of the primary amino group and the phenolic hydroxyl group of oxytocine to its biological activity has been investigated by the synthesis and study of desamino-desoxy-oxytocine, an analogue of the hormone lacking both of these functional groups. The desamino-desoxy-oxytocine was synthesized by reduction of S,S'-dibenzyl-desamino-desoxy-oxytocine.
(S-benzyl-β-mercapto-propionyl-L-phenylalanine-L-isoleucyl-L-glutaminy-L-asparaginy-S-benzyl-L-cysteinyl-L-prolyl-L-leucylglycinamide) with sodium in liquid ammonia and oxidation of the resulting dithiol to the cyclic disulfide with potassium ferricyanide. The S,S'-dibenzyl-desamino-desoxy-oxytocine was itself prepared by the stepwise p-nitrophenyl ester method. The desamino-desoxy-oxytocin was purified by countercurrent distribution, where its behavior showed it to be more lipophilic than desamino-oxytocin.

The desamino-desoxy-oxytocin possesses approximately one-eighth of the avian depressor activity, one-twentieth of the oxytocic activity, and one-tenth of the antidiuretic activity of oxytocin. In these activities it resembles desoxy-oxytocin.

The pressor activity of desamino-desoxy-oxytocin is lower than that of desoxy-oxytocin. Thus the pressor activity of oxytocin appears to decrease progressively upon removal of the primary amino group, the phenolic hydroxy group, and finally both of these groups.

It is of considerable interest that all the biological effects discussed herein are present to some degree in an analogue of oxytocin lacking both the primary amino and phenolic hydroxy group.

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