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Synthesis of 1-Hemi-D-cystine-oxytocin[1]

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1-Hemi-D-cystine-oxytocin, a diastereoisomer of oxytocin possessing the D-configuration in the half-cystine residue bearing the free amino group, has been synthesized. The compound was prepared by the stepwise *p*-nitrophenyl ester procedure and purified by countercurrent distribution. The hemi-D-cystine-oxytocin thus obtained possessed less than 2 units of avian depressor activity per mg., approximately $^1/_{250}$ that of oxytocin.

The synthesis of oxytocin,[3,4] the principal oxytocic and milk-ejecting hormone of the posterior pituitary gland, which contains all L-amino acids with the exception of glycine, has provided a means of studying the relationship of stereochemical structure to biological activity of oxytocin through the synthesis of diastereoisomers of the hormone. The first diastereoisomer that we undertook to synthesize was one possessing the D-configuration in the half-cystine residue bearing the free amino group. The preparation of this stereoisomer, isolated by countercurrent distribution, possessed appreciable biological activity. It was conceivable, however, that this activity might be attributable, at least in part, to contamination with a small amount of oxytocin possessing the hemi-L-cystine residue resulting from slight racemization of the hemi-D-cystine residue during the course of synthesis. This possibility had to be recognized, since the distribution coefficients of this hemi-D-cystine analog and oxytocin in countercurrent distribution were exceedingly close to one another. The availability of tritium-labeled oxytocin[5] offered an opportunity to label any oxytocin in the hemi-D-cystine-oxytocin preparation and thus to delineate the position of the oxytocin in the countercurrent distribution. The synthesis of this diastereoisomer with its isolation guided by this radioactive labeling technique is presented in this communication.

While this latter work was under way, Rudinger and his co-workers[6] reported the preparation of the compound, using, however, a different method of synthesis. Their protected nonapeptide upon reduction with sodium and liquid ammonia and subsequent oxidation yielded material having a slight activity which they noted may possibly have been due to contamination with a small amount of the "normal oxytocin."

In the course of our extended investigation of the 1-hemi-D-cystine-oxytocin, we took up the synthesis of a diastereoisomer bearing a D-amino acid in the side chain, 8-D-leucine-oxytocin.[7] In this instance the diastereoisomer had such a different distribution coefficient from that of oxytocin that it was possible to separate the two compounds completely. The 8-D-leucine-oxytocin was found to possess avian depressor and oxytocic activities of approximately 20 units per mg. and a milk-ejecting activity of at least 50 units per mg., and undoubtedly these activities represent inherent properties of this diastereoisomer.

For the synthesis of 1-hemi-D-cystine-oxytocin the protected nonapeptide N-carbobenzoxy-S-benzyl-D-cysteinyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-L-leucylglycinamide was prepared by the stepwise *p*-nitrophenyl ester procedure used previously in this Laboratory for the synthesis of oxytocin.[8] In the last step of the synthesis of the nonapeptide, *p*-nitrophenyl N-carbobenzoxy-S-benzyl-D-cysteinate replaced the *p*-nitrophenyl N-carbobenzoxy-S-benzyl-L-cysteinate used in the synthesis of oxytocin itself. The N-carbobenzoxy-S-benzyl-D-cysteine required for the preparation of this new *p*-nitrophenyl ester was made from S-benzyl-D-cysteine obtained through the resolution of N-formyl-S-benzyl-DL-cysteine with brucine.[9] The protected nonapeptide, obtained as an analytically pure, amorphous solid, was reduced with sodium in liquid ammonia to remove the carbobenzoxy and benzyl groups. After removal of the ammonia the reduced material thus obtained was aerated in aqueous solution at pH 6.8 for 5 hr. The oxidation was completed by treatment with potassium ferricyanide and the ferrocyanide ions were removed on a resin column as previously described[10] in the synthesis of deamino-oxytocin, formerly designated as desamino-oxytocin. Bioassay showed that 810 units of avian depressor activity were present. The solution was concentrated and approximately 1 mg. of tritium-labeled oxytocin[5] was added. The resulting solution possessed 30.6×10^3 counts per minute per unit of avian depressor activity. The solution was then subjected to countercurrent distribution in the system butanol–propanol–0.05% acetic acid (3:2:5) at 4° and the avian depressor activity, radioactivity, and Folin–Lowry color values were determined. After 800 transfers the radioactive peak ($K = 0.48$) was superimposed on the left side of the peak representing the hemi-D-cystine-oxytocin with a K value of 0.52 as determined by the Folin–Lowry color values. The bulk of the biological activity was present in the radioactive peak. After an additional 400 transfers, the contents of the tubes representing the Folin–Lowry peak were divided into two fractions, fraction 1 consisting of the contents of the 40 tubes to the left of the peak tube and fraction 2 consisting of the contents of the 40 tubes to the right of the peak tube. Thus fraction 1 contained hemi-D-cystine-oxytocin plus the labeled oxytocin and fraction 2 contained the hemi-D-cystine-oxytocin and very little radioactivity. Fraction 1 consisted of 9.75 mg. of solid containing 60 units of avian depressor activity per mg. and a specific activity of 1.97×10^6 counts per minute per mg. Fraction 2 consisted of 16.3 mg. of solid, possessing 2 units of avian depressor activity per mg. and a specific activity of 8.42×10^3 counts per minute per mg.

It is obvious from the results obtained through the use of labeled oxytocin as a marker in the countercurrent distribution purification of the hemi-D-cystine-oxytocin that there was a small amount of normal oxytocin present in the crude hemi-D-cystine-oxytocin derived from the protected nonapeptide intermediate and

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(3) V. du Vigneaud, C. Ressler, J. M. Swan, P. G. Katsoyannis, C. W. Roberts, and S. Gordon, *J. Am. Chem. Soc.*, **75**, 4879 (1953).

(4) V. du Vigneaud, C. Ressler, J. M. Swan, P. G. Katsoyannis, and C. W. Roberts, *ibid.*, **76**, 3115 (1954).

(5) V. du Vigneaud, C. H. Schneider, J. E. Stouffer, V. V. S. Murti, J. P. Aroskar, and G. Winestock, *ibid.*, **84**, 409 (1962).

(6) K. Jošt, J. Rudinger, and F. Šorm, *Collection Czech. Chem. Commun.*, **26**, 2496 (1961).

(7) C. H. Schneider and V. du Vigneaud, *J. Am. Chem. Soc.*, **84**, 3005 (1962).

(8) M. Bodanszky and V. du Vigneaud, *ibid.*, **81**, 5688 (1959).

(9) J. L. Wood and V. du Vigneaud, *J. Biol. Chem.*, **130**, 109 (1939).

(10) D. B. Hope, V. V. S. Murti, and V. du Vigneaud, *ibid.*, **237**, 1563 (1962).

one would suspect that the latter was not stereochemically pure but may have had a small amount of the S-benzyl-L-cysteine nonapeptide in it. The most likely step in the synthesis of the protected nonapeptide at which some degree of racemization might have occurred was in the condensation of the *p*-nitrophenyl N-carbobenzoxy-S-benzyl-D-cysteinate with the L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-L-leucylglycinamide. From the optical rotation of the N-carbobenzoxy-S-benzyl-D-cysteine one would have reason to believe that this starting material was stereochemically pure. Furthermore, the optical rotation of the crystalline nitrophenyl ester of this enantiomorph was numerically equal and opposite in sign to that of the L-isomer and we had no indication that racemization had occurred in the making of either ester. However, we have obtained some results in this Laboratory that the optical rotation of nitrophenyl esters of carbobenzoxy amino acids may decrease when they are allowed to stand in dimethylformamide in the presence of triethylamine, particularly so with that of N-carbobenzoxy-S-benzyl-L-cysteine.[11] This has been confirmed by Bodanszky and Birkhimer[12] who have also made additional observations in this connection. However, as pointed out by Bodanszky,[13] the rate of aminolysis of *p*-nitrophenyl N-carbobenzoxybenzylcysteinate is several magnitudes faster than the rate of racemization. Even though an excess of triethylamine was not employed in the condensation of *p*-nitrophenyl N-carbobenzoxy-S-benzyl-D-cysteinate with the S-benzyloctapeptide amide, it is conceivable that a slight degree of racemization might have occurred.

It should be noted that the tritium-labeled oxytocin[5] had been synthesized by the condensation of the pentapeptide, N-carbobenzoxy-S-benzyl-L-cysteinyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparagine, with the tetrapeptide, S-benzyl-L-cysteinyl-L-prolyl-L-leucylglycinamide. The pentapeptide had been synthesized by the coupling of crystalline N-carbobenzoxy-S-benzyl-L-cysteinyl-L-tyrosine with L-isoleucyl-L-glutaminyl-L-asparagine. The N-carbobenzoxy-S-benzyl-L-cysteinyl residue in the 1-position was not introduced by the nitrophenyl ester method so the possibility of racemization at this particular step does not apply to the tritium-labeled oxytocin. The slight radioactivity present in the hemi-D-cystine-oxytocin in fraction 2 may represent a slight contamination with the labeled normal oxytocin in the amount of about 0.06% on a weight basis. The results, however, demonstrate that the activity of the 1-hemi-D-cystine-oxytocin is as low as 2 units per mg. and perhaps somewhat lower. Further work is underway in an attempt to effect a complete separation of the hemi-D-cystine-oxytocin from oxytocin by other techniques, and establish whether even this low order of biological activity represents in whole or in part the inherent activity of the D-epimer. After this is accomplished the testing of 1-hemi-D-cystine-oxytocin for the presence of other biological activities characteristic of oxytocin will be carried out in conjunction with comparable studies on 6-hemi-D-cystine-oxytocin which is now in preparation.

The amino acid analysis of an acid hydrolysate of the hemi-D-cystine-oxytocin of fraction 2 was carried out according to the method of Spackman, Stein, and Moore[14] in the Beckman–Spinco amino acid analyzer and gave the expected amino acid ratios.

The striking effect of the spatial configuration of the amino group on the α-carbon of the 1-hemi-D-cystine residue is of particular interest in comparison with the high activity of the analog lacking the free amino group as in deamino-oxytoxin.[10] In other words, if the amino group be present, it must have the L-configuration. This would probably mean that when this asymmetric carbon is of the D-configuration the spatial arrangement of the amino group greatly hinders the functioning of the hormonal molecule. The avian depressor activity of the hemi-D-cystine-oxytocin is more comparable to those analogs bearing a substituent on the amino group of oxytocin where steric hindrance would appear to play a role.

Also of considerable interest is the dramatic effect of the D-configuration in the 1-position in contrast to the D-configuration in the 8-position of the side chain that is, 8-D-leucine-oxytocin. The latter analog, although less active than oxytocin itself, has ten times the avian depressor activity of the 1-hemi-D-cystine-oxytocin. Further exploration of the effect of the asymmetry of individual amino acid residues in oxytocin is under way, and it is hoped that such studies will cast further light on this aspect of the relationship of structure to the biological activity of this hormone. Furthermore, it is planned to synthesize the all-D-oxytocin, the optical isomer of the hormone, and in fact steps in this direction are under way.

Experimental[15]

N-Carbobenzoxy-S-benzyl-D-cysteine.—S-Benzyl-D-cysteine[9] (2.5 g.) was dissolved in *N* NaOH (15 ml.) and the solution was cooled in ice. Carbobenzoxy chloride (3 ml.) was added and the mixture was stirred for 1 hr. with the occasional addition of *N* NaOH to maintain the pH above 8.0. The ice bath was removed after 1 hr. while stirring was continued for an additional 2 hr. The sodium salt of the carbobenzoxy derivative separated as a heavy liquid which was dissolved in water (50 ml.), extracted twice with ether (50 ml.), and acidified with 5 *N* HCl, whereupon an oil separated. The carbobenzoxy derivative was extracted with ethyl acetate (3 × 80 ml.) and the extract was dried over anhydrous magnesium sulfate and concentrated to 20 ml. Hexane (200 ml.) brought about the separation of an oil which solidified upon being cooled to 4°. The solid material was collected, washed with hexane, and extracted with hot benzene (100 ml.) from a small amount of insoluble material (0.3 g.). The extract was concentrated to a smaller volume (10 ml.) and cooled to 4°. A white, crystalline product separated; wt. 2 g., m.p. 93–94°, $[\alpha]^{22}D$ +45° (*c* 4, absolute ethanol), which agrees numerically with the rotation of an authentic sample of the L-isomer under the same conditions. The melting point was unchanged after recrystallization from a mixture of ethyl acetate and hexane (1:3 v./v.). For analysis the product was dried at 78° *in vacuo* over P_2O_5 for 12 hr.

Anal. Calcd. for $C_{18}H_{19}O_4N_5$: C, 62.6; H, 5.54; N, 4.06. Found: C, 62.7; H, 5.67; N, 4.16.

***p*-Nitrophenyl N-Carbobenzoxy-S-benzyl-D-cysteinate.**—N-Carbobenzoxy-S-benzyl-D-cysteine (2.5 g.) and *p*-nitrophenol (1.6 g.) were dissolved in tetrahydrofuran (50 ml. freshly distilled from sodium) and the solution was cooled in an ice bath. Dicyclohexylcarbodiimide (1.8 g.) was added with stirring. The stirring was continued for 1 hr. at 0° and for an additional 2 hr. at room temperature. The dicyclohexylurea formed was removed by filtration and washed with tetrahydrofuran. The filtrate and washings were concentrated and the yellow, viscous residue was dissolved in warm ethanol (10 ml.). When the solution was cooled, a crystalline solid separated. This after two recrystallizations from ethanol amounted to 1.9 g., m.p. 92–93°, $[\alpha]^{22}D$ +44.5° (*c* 1, dimethylformamide); lit. (L-isomer) −42° (*c* 1, dimethylformamide)[16]; $[\alpha]^{20}D$ −43° (*c* 2, dimethylformamide).[8]

Anal. Calcd. for $C_{24}H_{22}O_6N_2S$: C, 61.8; H, 4.75; N, 6.01. Found: C, 61.8; H, 4.84; N, 6.04.

N-Carbobenzoxy-S-benzyl-D-cysteinyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-L-leueylglycinamide.—N-Carbobenzoxy-O-benzyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-L-leucylglycinamide[8] (0.8 g.) was suspended in dry glacial acetic acid (10 ml.), hydrogen bromide in acetic acid (35% w./w., 10 ml.) was added, and the mixture was stirred mechanically at

(11) J. Stouffer, D. Jarvis, and V. du Vigneaud, unpublished observations; referred to by M. Bodanszky (see ref. 13).

(12) M. Bodanszky and C. A. Birkhimer, *Chimia*, **14**, 368 (1960).

(13) M. Bodanszky, *Ann. N. Y. Acad. Sci.*, **88**, 655 (1960).

(14) D. H. Spackman, W. H. Stein, and S. Moore, *Anal. Chem.*, **30**, 1190 (1958).

(15) All melting points are corrected capillary melting points.

(16) M. Bodanszky and V. du Vigneaud, *J. Am. Chem. Soc.*, **81**, 2504 (1959).

room temperature for 1.5 hr. Dry ether (300 ml.) was added to the clear solution and the solid hydrobromide was collected and washed with dry ether. The dry hydrobromide was dissolved in dimethylformamide (20 ml.), neutralized with triethylamine, and coupled with *p*-nitrophenyl N-carbobenzoxy-S-benzyl-D-cysteinate (0.6 g.). The mixture was stirred for 3 days. Methanol (300 ml.) was added, the solid collected, washed with methanol (150 ml.) and ethyl acetate (150 ml.), and dried in a vacuum desiccator over P_2O_5. Further purification was effected by solution in dimethylformamide, filtration, and reprecipitation with ethyl acetate; wt. 0.5 g., m.p. 237–238° dec., sintering at 230°, $[\alpha]^{20}D$ −32° (*c* 1, dimethylformamide). For analysis the compound was dried *in vacuo* at 100° for 20 hr.

Anal. Calcd. for $C_{65}H_{86}O_{14}N_{12}S_2$: C, 59.0; H, 6.55; N, 12.7. Found: C, 58.8; H, 6.55; N, 12.5.

1-Hemi-D-cystine-oxytocin Isolated by Countercurrent Distribution after Admixture with Tritium-Labeled Oxytocin.—The dry protected nonapeptide intermediate (156 mg.) was dissolved in liquid ammonia (300 ml.), freshly distilled from sodium, and treated with sodium after removal of the acetone–Dry Ice bath until a persistent blue color appeared in the solution. After 5 min. glacial acetic acid (0.5 ml.) was added and the volume of ammonia was reduced to between 15 and 20 ml. in a stream of dry, oxygen-free nitrogen, the remaining ammonia being removed by lyophilization. The residue was taken up in distilled water (250 ml.). This solution, containing 800 units of avian depressor activity, was aerated at pH 6.8 for 5 hr. The nitroprusside test for thiols showed that the hemi-D-cystine-oxytoceine was incompletely oxidized and this process was completed by adding potassium ferricyanide solution until a yellow color appeared in the solution (10.3 ml. of 0.011 *N* $K_3Fe(CN)_6$). The ferrocyanide and ferricyanide ions were removed on a column (0.9 cm. × 15 cm.) of ion-exchange resin AG 3X4 in chloride form as previously described. The eluates and washings from this column were combined to give a solution containing 810 units of avian depressor activity. This solution was evaporated *in vacuo* below room temperature to a volume of 10 ml. and mixed with 10 ml. of a solution containing radioactive oxytocin (370 units of avian depressor activity, with a specific activity of 96.5 × 10^3 counts per minute per unit).[5,17] The combined solution containing 1180 units of avian depressor activity and a specific activity of 30.6 × 10^3 counts per minute per unit was placed in the first 10 tubes of a 6-ml. 400-tube Craig countercurrent machine and subjected to a total of 1,200 transfers in the solvent system butanol–propanol–0.05% acetic acid (3:2:5) at 4°. After 800 transfers a separation into three peaks with *K* values of 0.22, 0.35, and 0.52 had been accomplished, as detected by the Folin–Lowry color reaction.[18] The oxytocin formed a distinct peak with a *K* value of 0.48 as detected by determination of radioactivity. Apart from a trace of radioactive material traveling with a *K* value of 0.21, the peak due to oxytocin accounted for almost all the radioactivity and biological activity. After 1,200 transfers (with recycling) a small shoulder could be detected with the Folin–Lowry reaction on the following edge of the fast-moving peak corresponding in position to the peak in the distribution of radioactivity and of biological activity (*K* = 0.46) presumably due to oxytocin. A fraction (tubes 360–400) was taken from this area to include as much as possible of the radioactive and biologically active material. Similarly, the contents of tubes 0–40 (after recycling) containing the hemi-D-cystine-oxytocin (K = 0.50) were collected and combined. These two fractions were evaporated *in vacuo* and lyophilized to give 9.75 and 16.3 mg. of solid material, respectively. On assay the oxytocin-containing fraction showed 60 units of avian depressor activity per mg. The specific activity on a unit basis was 32.2 × 10^3 counts per minute per unit compared with 30.6 × 10^3 counts per minute per unit initially.

An amino acid analysis of a sample of the hemi-D-cystine-oxytocin after acid hydrolysis was performed on a Beckman–Spinco amino acid analyzer according to the procedure of Spackman, Stein, and Moore[14] using the 30–50° system. The following amino acid molar ratios (isoleucine taken as 1) were obtained: aspartic acid 1.0, glutamic acid 1.0, proline 1.0, glycine 1.0, half-cystine 0.8, half-mesocystine 0.7, leucine 1.0, isoleucine 1.0, tyrosine 0.6, and ammonia 3.0.

The molecular weight of the hemi-D-cystine-oxytocin was kindly determined by Dr. David Yphantis of the Rockefeller Institute, by use of short column equilibrium centrifugation. At concentrations ranging from 0.25 to 1% in 0.15 *M* ammonium acetate at pH 5.57 the average molecular weight was 1070 ± 70, assuming a partial specific volume of 0.71.

The hemi-D-cystine-oxytocin on bioassay for avian depressor activity according to the method of Munsick, Sawyer, and van Dyke[19] showed 2.0 units of avian depressor activity per mg. (average of three four-point assays). The material also showed a very low level of radioactivity; the specific activity was 4.21 × 10^3 counts per minute per unit of avian depressor activity.

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(17) Liquid scintillation counting was carried out in a Tracerlab scintillation counter using the dioxane–xylene phosphor of Jacobsen, Gupta, and Fernandez (*Arch. Biochem. Biophys.*, **86**, 89 (1960)); 10 ml. of phosphor solution was added to 5 ml. of dioxane solution containing the active sample (usually 100 μl. of an aqueous solution). The efficiency was between 12 and 14% and was controlled with tritiated toluene (New England Nuclear Corp.) as an internal standard.

(18) O. H. Lowry, N. J. Rosebrough, A. L. Farr, and R. J. Randall, *J. Biol. Chem.*, **193**, 265 (1951).

(19) R. A. Munsick, W. H. Sawyer, and H. B. van Dyke, *Endocrinol.*, **66**, 860 (1960).

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Mass Spectrometry in Structural and Stereochemical Problems. XXXII.[1] Pentacyclic Triterpenes

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Mass spectra were measured of saturated and unsaturated members of the α- and β-amyrin group as well as of representatives of the taraxerol, bauerene, friedelane, and lupane series. Assignments have been made to the principal fragments and, in most instances, plausible mechanisms are proposed to rationalize the formation of these ions. In general, the presence of a nuclear double bond controls the fragmentation behavior, and characteristic mass spectral features have been noted which frequently allow assignment of membership of a given triterpene in one of the major classes by this criterion. In addition, the location of functional groups can often be narrowed down by consideration of the fragmentation pattern. Mass spectrometry thus constitutes an extremely useful physical method in the triterpene field and, when combined with rotatory dispersion measurements of derived ketones, can lead to structure elucidation with a minimum quantity of material.

Mass spectrometry has been used during the last few years to an increasing extent for the structure elucidation of complex polycyclic natural products, especially alkaloids[2,3] and steroids.[4] Very little work has been done so far in the pentacyclic triterpene field[5a] because of the low volatility of these compounds which requires

(1) For paper XXXI see M. Ohashi, J. M. Wilson, H. Budzikiewicz, M. Shamma, W. A. Slusarchyk, and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 2807 (1963).

(2) (a) K. Biemann, "Mass Spectrometry," McGraw-Hill Book Co., Inc., New York, N. Y., Chapter 8; (b) C. Djerassi, *Pure Appl. Chem.*, **6**, 575 (1963).

(3) C. Djerassi, H. Budzikiewicz, R. J. Owellen, J. M. Wilson, W. G. Kump, D. J. Le Count, A. R. Battersby, and H. Schmid, *Helv. Chim. Acta*, **46**, 742 (1963), and previous papers cited therein.

(4) D. H. Williams, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 2091 (1963), and previous papers cited therein.

(5) (a) P. de Mayo and R. I. Reed, *Chem. Ind.* (London), 1481 (1956); R. I. Reed, *J. Chem. Soc.*, 3432 (1958). (b) Very recently, J. L. Courtney, and J. S. Shannon, *Tetrahedron Letters*, 13, 173 (1963), have reported a detailed mass spectrometric study of friedelane derivatives. (c) NOTE