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Synthesis of 1-L-Penicillamine-oxytocin, 1-D-Penicillamine-oxytocin, and 1-Deaminopenicillamine-oxytocin, Potent Inhibitors of the Oxytocic Response of Oxytocin[1]

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1-L-Penicillamine-oxytocin has been prepared by reaction of *p*-nitrophenyl N-carbobenzoxy-S-benzyl-L-penicillaminate with L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-L-leucylglycinamide followed by reduction of the resulting protected nonapeptide with sodium in liquid ammonia and oxidation to the cyclic disulfide. In the 1-L-penicillamine-oxytocin the β carbon of the half-cystine residue at position 1 of the hormone is substituted by two methyl groups. 1-L-Penicillamine-oxytocin and 1-D-penicillamine-oxytocin were both obtained by separation through partition chromatography on Sephadex of the diastereoisomeric analogs resulting from a similar series of reactions starting with N-carbobenzoxy-DL-penicillaminate. In addition, 1-deaminopenicillamine-oxytocin was synthesized, with the use of β-benzylmercaptoisovaleric acid in place of N-carbobenzoxy-S-benzylpenicillamine. All three of these analogs were found to be devoid of avian vasodepressor, oxytocic, and pressor activities. On the other hand, they possessed inhibitory activity on the avian depressor and oxytocic activities of oxytocin. The 1-L-penicillamine-oxytocin and 1-deaminopenicillamine-oxytocin were particularly potent inhibitors of the oxytocic activity of the hormone. The D analog was less potent than the L compound.

As a further study of the importance of the specificity of the structure of the amino acid residue at position 1 in oxytocin (Figure 1) to its pharmacological behavior, we thought it would be of interest to ascertain the pharmacological properties of an analog of oxytocin in which the half-cystine residue at position 1 of oxytocin is replaced by that of L-penicillamine. Thus, the two hydrogens attached to the β carbon of the half-cystine residue at position 1 would be substituted by two methyl groups. We have therefore prepared 1-L-penicillamine-oxytocin along with its diastereoisomer, 1-D-penicillamine-oxytocin. In addition, we have synthesized 1-deaminopenicillamine-oxytocin (1-β-mercaptoisovaleric acid-oxytocin).

Since it has been found in this laboratory that oxytocin and its diastereoisomer, 1-hemi-D-cystine-oxytocin, can be separated from one another[2] both by partition chromatography on Sephadex and by countercurrent distribution, there seemed to be a good possibility that one might be able to obtain both 1-L-penicillamine-oxytocin and 1-D-penicillamine-oxytocin starting from DL-penicillamine. For the preparation of these two diastereoisomeric analogs, the protected octapeptide amide N-carbobenzoxy-O-benzyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-L-leucylglycinamide (I), prepared by the stepwise nitrophenyl ester method, served as starting material.[3] The nitrophenyl ester of N-carbobenzoxy-S-benzyl-DL-penicillamine was allowed to react with the free S-benzyloctapeptide amide (II) obtained from the protected octapeptide amide (I) by removal of the N-carbobenzoxy and O-benzyl groups with hydrogen bromide in trifluoroethanol. The resulting mixture of the two diastereoisomeric protected nonapeptides was subjected to treatment with sodium in liquid ammonia by the method of Sifferd and du Vigneaud,[4] as used in the synthesis of oxytocin[5] to cleave the N-carbobenzoxy and S-benzyl groups. The resulting disulfhydryl compounds were oxidized to the cyclic disulfides in neutral aqueous solution with potassium ferricyanide.[6] After removal of the ferricyanide and ferrocyanide ions, the crude mixture of the diastereoisomeric cyclic octapeptide amides was freed of gross impurities by subjection to countercurrent distribution[7] in the solvent system 1-butanol–pyridine–benzene–0.1% aqueous acetic acid (6:1:2:9). The material in the peak with a K value of 1.4 representing the two octapeptide amide analogs was isolated and subjected to partition chromatography on Sephadex G-25[8] in the solvent system 3.5% aqueous acetic acid (containing 1.5% pyridine)–1-butanol (1:1) in which a separation of the two diastereoisomeric analogs was achieved. Two peaks were ob-

(1) This work was supported in part by Grant HE-01675 from the National Heart Institute, U. S. Public Health Service.

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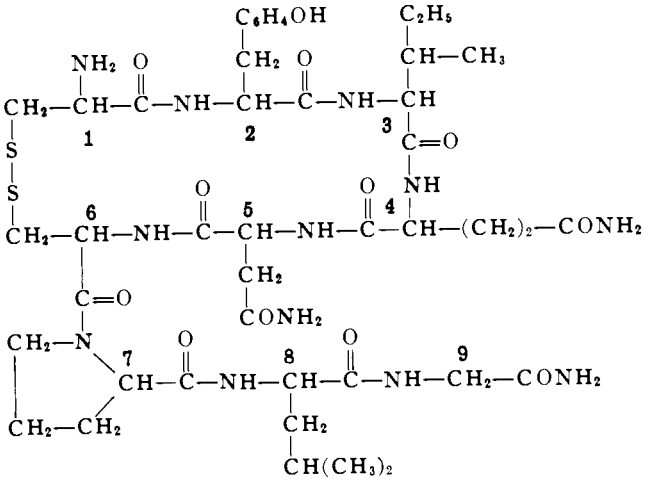

Figure 1.—Structure of oxytocin, with numbers indicating the position of the individual amino acid residues.

tained as determined by the Folin–Lowry color values,[9] one with an R_f of 0.29 and the other with an R_f of 0.46. In order to establish the identity of the diastereoisomers represented by the two peaks, L-penicillamine-oxytocin was prepared. With the use of this authentic sample the peak with an R_f of 0.29 was established as representing the L analog. The 1-D-penicillamine-oxytocin (R_f 0.46) was subjected to further purification. The material was rechromatographed on Sephadex G-25 in the solvent system 3.5% aqueous acetic acid (containing 1.5% pyridine)–1-butanol–benzene (9:1:10) (R_f 0.31).

It is interesting to note that of the two penicillamine analogs the diastereoisomer containing the D amino acid residue is more soluble in the organic phase in countercurrent distribution and partition chromatography as in the case of 1-hemi-D-cystine-oxytocin and oxytocin.[2] This same relationship with respect to the greater solubility in the organic phase of the D diastereoisomer in comparison with that of oxytocin was also found to be true of 2-D-tyrosine-oxytocin,[10] 5-D-asparagine-oxytocin,[11] 4-D-glutamine-oxytocin,[11] 6-hemi-D-cystine-oxytocin,[12] 7-D-proline-oxytocin,[13] and 8-D-leucine-oxytocin.[14]

For the preparation of the 1-L-penicillamine-oxytocin, *p*-nitrophenyl N-carbobenzoxy-S-benzyl-L-penicillaminate was allowed to react with the aforementioned free S-benzyloctapeptide amide (II). The resulting nonapeptide N-carbobenzoxy-S-benzyl-L-penicillaminyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-L-leucylglycinamide was reduced and oxidized as described for the mixture of the two diastereoisomeric nonapeptides. The purification was carried out by countercurrent distribution in the solvent system 1-butanol–pyridine–benzene–0.1% aqueous acetic acid (6:1:2:9) (K, 1.25), followed by partition chromatography on Sephadex G-25 in the solvent system 3.5% aqueous acetic acid (containing 1.5% pyridine)–1-butanol (1:1) (R_f 0.27).

For the preparation of 1-deaminopenicillamine-oxytocin, β-benzylmercaptoisovaleric acid was required. This compound was prepared by a nucleophilic addition of benzylmercaptan to 3,3-dimethylacrylic acid in the presence of piperidine.[15] The nitrophenyl ester of this acid was allowed to react with the free octapeptide (II). The resulting compound was reduced and oxidized as described for the penicillamine analogs. The crude material was purified by countercurrent distribution in the solvent system 0.5% aqueous acetic acid (containing 0.1% pyridine)–1-butanol–benzene (5:3:2). 1-Deaminopenicillamine-oxytocin, which has a partition coefficient of 2 in this solvent system, was isolated by evaporation followed by lyophilization of the contents of the tubes representing the peak.

The penicillamine analogs were assayed for avian vasodepressor,[16] rat oxytocic,[17] and rat pressor[18] activities. All three analogs were found to be devoid of the specific activities assayed. Moreover, they were found to possess inhibitory activity on the avian vasodepressor and rat oxytocic responses to highly purified synthetic oxytocin (500 units/mg).

These three analogs showed only a slight inhibitory effect on the avian vasodepressor activity of oxytocin. Generally a molar ratio of 100:1 to 200:1 (analog:oxytocin) was required to produce a clear-cut inhibition on the depressor response to oxytocin over the range of 30–60 milliunits of oxytocin, the normal dose range used in the avian vasodepressor assays.

On the other hand, both 1-L-penicillamine-oxytocin and 1-deaminopenicillamine-oxytocin were highly potent inhibitors of the oxytocic activity of oxytocin. When tested on the isolated rat uterus, as small a molar ratio as 2.5:1 could produce a marked inhibition on the oxytocic response to oxytocin over the range of 5–10 milliunits of oxytocin, the normal dose range used in the rat oxytocic assays. 1-D-Penicillamine-oxytocin was about one-tenth as inhibitory as the 1-L-penicillamine-oxytocin and the 1-deaminopenicillamine-oxytocin.

In *in vivo* rat preparations in which rhythmic contractions of the uterus were induced by a continuous infusion of oxytocin, simultaneous infusion of either the 1-L-penicillamine-oxytocin or its deamino analog completely suppressed the uterine motility.

These preliminary pharmacological studies on the oxytocic inhibitory activity of these two penicillamine analogs suggest that the inhibitory activity is specific against only those polypeptides structurally related to the neurohypophysial hormones and that the inhibition is competitive and reversible in nature. Further investigations are now being carried out on the pharmacology of these analogs of oxytocin and deamino-oxytocin.

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Experimental Section[19]

N-Carbobenzoxy-S-benzyl-L-penicillamine was prepared in 96% yield by use of the procedure described by Marshall, *et al.*,[20] for N-carbobenzoxy-S-benzyl-DL-penicillamine, $[\alpha]^{20}D$ −7.1° [*c* 2, dimethylformamide (DMF)].

Anal. Calcd for $C_{20}H_{23}NO_4S$: C, 64.3; H, 6.21. Found: C, 63.8; H, 6.20.

***p*-Nitrophenyl N-Carbobenzoxy-S-benzyl-L-penicillaminate.**—N-Carbobenzoxy-S-benzyl-L-penicillamine (6 g) and *p*-nitrophenol (2.7 g) were dissolved in 15 ml of ethyl acetate and cooled to 0°. Dicyclohexylcarbodiimide (3.3 g) was then added and the solution was stirred for 1 hr at 0° and overnight at room temperature. The suspension was acidified with 1 *N* HCl (10 ml) and the N,N'-dicyclohexylurea was collected by filtration. The aqueous phase was separated and the organic phase was dried ($MgSO_4$) and evaporated. The oily residue was dissolved in 40 ml of chloroform and passed through a silica gel column. The eluate was evaporated *in vacuo* at 80°; 6.8 g, $[\alpha]^{20}D$ +12° (*c* 2, DMF).

Anal. Calcd for $C_{26}H_{26}N_2O_6S$: C, 63.1; H, 5.30. Found: C, 63.3; H, 5.59.

N-Carbobenzoxy-S-benzyl-L-penicillaminyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-L-leucylglycinamide.—N-Carbobenzoxy-O-benzyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-L-leucylglycinamide (0.9 g) was suspended in trifluoroethanol (25 ml) and HBr was bubbled through for 30 min. The solvent was evaporated, and the residue was washed three times with ether, dried over KOH, and then dissolved in 5 ml of DMF. The pH was adjusted to 8 with triethylamine and a solution of 0.75 g of *p*-nitrophenyl N-carbobenzoxy-S-benzyl-L-penicillaminate in 6 ml of DMF was added. After the mixture was stirred for 2 days 100 ml of ethyl acetate was added. The precipitate was filtered off, treated with 60 ml of ethanol and 60 ml of ethyl acetate, and finally dried; yield 0.7 g. For analytical purposes the substance was reprecipitated from DMF–ethyl acetate and from tetrahydrofuran (THF)–water; $[\alpha]^{20}D$ −44.5° (*c* 1.2, DMF), mp 224–228°.

Anal. Calcd for $C_{67}H_{90}N_{12}O_{14}S_2$: C, 59.5; 6.71; N, 12.4. Found: C, 59.2; H, 6.72; N, 12.5.

1-L-Penicillamine-oxytocin.—N-Carbobenzoxy-S-benzyl-L-penicillaminyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-L-leucylglycinamide (0.24 g) was dissolved in 40 ml of anhydrous liquid ammonia and reduced with sodium until the blue color lasted for 30 sec. The NH_3 was removed by evaporation and lyophilization. The white residue was dissolved in 250 ml of deaerated 0.1% acetic acid, the pH was adjusted to 7.0, and the theoretical amount of 0.01 *N* potassium ferricyanide solution (35.4 ml) was added. The yellow solution was passed through a column containing an ion-exchange resin in the chloride form [Rexyn C6 (8) Cl]. The eluate was concentrated to 25 ml, placed in the first three tubes of a countercurrent distribution machine, and subjected to 200 transfers in the solvent system 1-butanol–pyridine–benzene–0.1% acetic acid (6:1:2:9). The distribution curve obtained from the Folin–Lowry color values showed two peaks. The larger peak advancing with the upper phase with an extremely high *K* value, consisted of a mixture of by-products. The central portion of the smaller peak (K_1 1.25) was evaporated and lyophilized; 47 mg. This material was subjected to partition chromatography on Sephadex G-25 in the solvent system 3.5% aqueous acetic acid (containing 1.5% pyridine)–1-butanol (1:1). The compound emerged as a single peak with an R_f of 0.27. The central part of the peak gave 31 mg of 1-L-penicillamine-oxytocin, $[\alpha]^{20}D$ +18° (*c* 0.5, 1 *N* acetic acid). A small sample subjected to gel filtration on Sephadex G-25 in the solvent 0.2 *N* acetic acid gave one symmetrical peak close to the position established for that of oxytocin. On electrophoresis and paper chromatography the compound showed only one spot. For analysis a sample was dried (P_2O_5) at 100° *in vacuo* and a loss in weight of 5.8% was observed.

Anal. Calcd for $C_{45}H_{70}N_{12}O_{12}S_2$: C, 52.2; H, 6.82; N, 16.2. Found: C, 52.0; H, 6.81; N, 15.9.

1-D-Penicillamine-oxytocin.—N-Carbobenzoxy-O-benzyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-L-leucylglycinamide (1.4 g) was suspended in trifluoroethanol (15 ml) and treated with HBr for 0.5 hr. The solvent was removed by evaporation, and the residue was washed with ether three times and then dissolved in 5 ml of DMF. The pH was adjusted to 7.5 with triethylamine and a solution of 1 g of *p*-nitrophenyl N-carbobenzoxy-DL-penicillaminate, prepared as described for the L isomer, in 6 ml of DMF was added. After the solution was stirred for 2 days the reaction product was precipitated with 70 ml of ethyl acetate and further purified by washing with 70 ml of ethanol and 70 ml of ethyl acetate; 1.2 g. The sample was reprecipitated from THF–water; 0.7 g, mp 226–230°.

The compound (290 mg) was dissolved in anhydrous liquid ammonia and treated with sodium until the blue color lasted for 15 sec. The NH_3 was removed by evaporation followed by lyophilization and the residue was dissolved in 300 ml of 0.1 *N* acetic acid. The pH was adjusted to 6.8 and 0.01 *N* potassium ferricyanide solution (40 ml) was added. The solution was passed through a column containing an ion-exchange resin in the chloride form [Rexyn CG (8) Cl]. The filtrate was concentrated to a volume of 60 ml, placed in the first six tubes of a countercurrent distribution machine and subjected to 200 transfers in the solvent system 1-butanol–benzene–pyridine–0.1% aqueous acetic acid (6:2:1:9). A distribution curve as determined by the Folin–Lowry color values showed two peaks, a large one advancing with the upper phase with an extremely high *K* value which consisted of various by-products, and a smaller one with a *K* value of 1.4, from which the material was isolated by evaporation and lyophilization. This material (35 mg) was subjected to partition chromatography on Sephadex G-25 in the solvent system 3.5% aqueous acetic acid (containing 1.5% pyridine)–1-butanol (1:1). The Folin–Lowry curve showed two peaks with R_f values of 0.46 and 0.29. The contents of the tubes representing the peak with an R_f of 0.29 were evaporated and lyophilized to yield 8 mg of L-penicillamine-oxytocin.

The contents of the tubes representing the peak with an R_f of 0.46 were evaporated and lyophilized to yield 13 mg of D-penicillamine-oxytocin. The entire procedure was repeated with the use of a larger amount of the nonapeptides made with DL-penicillamine. The contents of the tubes representing the D-penicillamine-oxytocin from the partition chromatography on Sephadex were evaporated to yield 22 mg of the D analog. This material was then subjected to rechromatography on Sephadex G-25 in the solvent system 3.5% aqueous acetic acid (containing 1.5% pyridine)–1-butanol–benzene (10:9:1). The D-penicillamine-oxytocin was obtained in a sharp peak with an R_f value of 0.31. The contents of the tubes representing this peak on concentration and lyophilization yielded 18.5 mg of the analog. On electrophoresis and paper chromatography the compound showed only one spot. When the compound was subjected to gel filtration on Sephadex G-25 in the solvent 0.2 *N* acetic acid, it emerged as a single peak at the same position as the L analog. The rotation of 1-D-penicillamine-oxytocin was $[\alpha]^{20}D$ −28° (*c* 0.5, 1 *N* acetic acid).

β-Benzylmercaptoisovaleric Acid.—3,3-Dimethylacrylic acid (8 g), benzylmercaptan (9.4 ml), and piperidine (12 ml) were refluxed for 13 hr. The reaction mixture was then acidified with HCl and extracted three times with ether. The combined ether extracts were subsequently treated with a concentrated $NaHCO_3$ solution until the evolution of CO_2 ceased. The combined aqueous phases were acidified with HCl and extracted with ether. After the extracts were dried (Na_2SO_4), the solvent was removed by evaporation and the oily residue was distilled under reduced pressure; bp 194–195° (12 mm), 5.4 g. To remove traces of benzylmercaptan the substance was dissolved in a concentrated solution of $NaHCO_3$, washed with ether, acidified, and extracted with ether. The solvent was removed *in vacuo* at 100°.

Anal. Calcd for $C_{12}H_{16}O_2S$: C, 64.2; H, 7.19. Found: C, 64.4; H, 7.14.

***p*-Nitrophenyl β-benzylmercaptoisovalerate,** mp 54.5–55.5°, was prepared in 50% yield according to the procedure described for *p*-nitrophenyl N-carbobenzoxy-S-benzyl-L-penicillaminate. After recrystallization from methanol the ester melted at 55–56°.

Anal. Calcd for $C_{18}H_{19}NO_4S$: C, 62.6; H, 5.54; N, 4.06. Found: C, 62.8; H, 5.59; N, 4.06.

β-Benzylmercaptoisovaleryl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-L-leucylglycinamide.—N-Carbobenzoxy-O-benzyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-L-leucylgly-

(19) Capillary melting points were determined and are corrected. Paper chromatography was performed on Whatman No. 1 paper in 1-butanol–acetic acid–water (4:1:5, descending), and Pauly reagent was used for development. Paper electrophoresis was carried out at 4° for 22 hr in pyridine acetate buffer of pH 5.6 at 300 v, and Pauly reagent was used for development.

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cinamide (0.6 g) was suspended in 10 ml of trifluoroethanol and HBr was bubbled through for 30 min. The clear solution was kept for another hour at room temperature. The solvent was evaporated and the residue was washed with ether three times. The dried residue was dissolved in 6 ml of DMF and the pH was adjusted to 8 with triethylamine. *p*-Nitrophenyl β-benzylmercaptoisovalerate (0.35 g) was added and the solution was stirred for 4 days at room temperature. The semisolid mixture was treated successively with 80 ml of ethyl acetate, 40 ml of ethanol, and 40 ml of ethyl acetate and finally washed on the filter with 40 ml of ethyl acetate; 0.51 g. This material was used to prepare the analog. For analytical purposes the substance was reprecipitated from DMF–ethyl acetate and from THF–water; mp 234–237°, $[\alpha]^{20}D$ −48.5° (c 1, DMF).

Anal. Calcd for $C_{59}H_{83}N_{11}O_{12}S_2$: C, 58.9; H, 6.96; N, 12.8. Found: C, 58.7; H, 7.01; N, 12.6.

1-Deaminopenicillamine-oxytocin (1-β-Mercaptoisovaleric Acid-oxytocin).—β-Benzylmercaptoisovaleryl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-L-leucylglycinamide (0.23 g) was dissolved in 50 ml of anhydrous liquid ammonia and reduced with sodium until the blue color lasted for a few seconds. The ammonia was removed by evaporation and lyophilization. The resulting white residue was dissolved in 230 ml of deaerated water, the pH was adjusted to 6.8 with acetic acid, and the theoretical amount of a 0.01 *N* potassium ferricyanide solution (38 ml) was added. The solution was deionized by passage through a column containing the ion-exchange resin [Rexyn CG (8) Cl] in the chloride form. The filtrate was concentrated to 50 ml, placed in the first five tubes of a countercurrent distribution machine, and subjected to 400 transfers in the solvent system 0.5% aqueous acetic acid (containing 0.1% pyridine)–1-butanol–benzene (5:3:2). A main peak with a *K* value of 2 was obtained as determined by the Folin-Lowry color values. Concentration and lyophilization of the fractions from the central part of the peak yielded 78 mg of 1-deaminopenicillamine-oxytocin with an optical rotation of $[\alpha]^{20}D$ −53.6° (c 0.5, 1 *N* acetic acid).

A small amount of this compound was subjected to gel filtration on Sephadex G-25 in the solvent 0.2 *N* acetic acid. A single peak emerged at the position of oxytocin. On paper chromatography the compound showed only one spot. For analysis a sample was dried (P_2O_5) at 100° *in vacuo* and a loss in weight of 6.5% was observed.

Anal. Calcd for $C_{45}H_{69}N_{11}O_{12}S_2$: C, 53.0; H, 6.82; N, 15.1. Found: C, 52.9; H, 6.92; N, 14.9.

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Relationship between Configuration and Adrenergic β-Receptor Blocking Activity of Optical Isomers of 1-(4-Nitrophenyl)-2-isopropylaminoethanol (INPEA)

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1-(4-Nitrophenyl)-2-isopropylaminoethanol (INPEA), a highly specific adrenergic β-receptor inhibitor, has been resolved into its optically active isomers. Pharmacologically it has been shown that only the levorotatory isomer displays β-receptor blocking activity. The optically pure dextrorotatory isomer was found to be completely inactive even at very high doses. The absolute D configuration of the active isomer was chemically determined.

Pharmacologically, 1-(4-nitrophenyl)-2-isopropylaminoethanol (INPEA) has been shown to be an effective adrenergic β-receptor antagonist.[2-8] Clinically, INPEA has been shown to be of potential value in the treatment of various disorders.[9-12] The value of INPEA lies in its lack of local anesthetic activity and freedom from intrinsic sympathomimetic activity.

To improve the pharmacological and clinical utility of INPEA, we have prepared the two optical isomers of INPEA[13] and established chemically their absolute configuration.

Resolution of INPEA was achieved by fractional crystallization of the salt of D-(−)-dibenzoyltartaric acid. The less soluble (+)-INPEA D-(−)-dibenzoyltartrate was easily purified by recrystallization from ethanol. From the mother liquors, (−)-INPEA D-(−)-dibenzoyltartrate was obtained.

To establish the absolute configuration at the asymmetric center, (−)-INPEA was converted into (−)-1-(4-hydroxyphenyl)-2-isopropylaminoethanol (V); this last compound was also prepared, starting from (D-(−)-1-(4-hydroxyphenyl)-2-aminoethanol (D-(−)-octopamine, VI), the absolute configuration of which is known.[14,15] Scheme I shows these reactions.

The absolute values of rotation of (−)-V obtained *via* the two routes were not equal, due to the facile racemization of the diazonium fluoroborate, (+)-IV, during its hydrolysis to (−)-V.

To establish that reductive condensation of the optical isomers of phenylethanolamines with ketones does not influence rotation, (−)-1-(4-methoxyphenyl)-2-aminoethanol, (−)-1-(3-hydroxyphenyl)-2-aminoethanol,[16] and (−)-1-(4-aminophenyl)-2-aminoethanol[17] were synthesized and reductively alkylated with acetone or 2-butanone. We obtained (−)-1-(4-methoxyphenyl)-2-isopropylaminoethanol, (−)-1-(3-hydroxy-

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