was added, and gaseous HCl was introduced into the filtrate. The formed precipitate was filtered off and recrystallized from a mixture of 100 ml. of methanol and 20 ml. of water, to give 2.6 g. of **33**.

Acknowledgment.—The authors are indebted to Mr. P. Demoen and co-workers for the analysis of the compounds. The work described in this publication is part of a program on piperidine derivatives, supported by a grant from the Instituut tot Aanmoediging van het Wetenschappelijk Onderzoek in Nijverheid en Landbouw (IWONL).

(−)-5-Ethyl-5-phenyl-2-pyrrolidinone. Unusual Reactions of 4-Nitro-4-phenylhexanoic Acid

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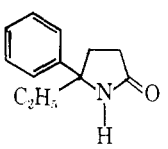
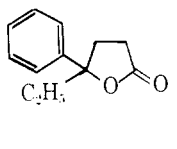
(−)-5-Ethyl-5-phenyl-2-pyrrolidinone has been synthesized from 4-nitro-4-phenylhexanoic acid, the reduction of which with titanous chloride gave 3-benzoylpropionic acid, propiophenone, and 4-ethyl-4-phenyl-γ-butyrolactone. The pharmacological properties of the (−)-lactam did not differ sufficiently from those of the racemic mixture to warrant preparing the (+)-isomer.

During the evaluation of a series of lactams prepared by Professor W. Taub as potential sedative hypnotics, 5-ethyl-5-phenyl-2-pyrrolidinone (I) proved to be of particular interest. The presence in the lactam of an asymmetric center suggested the examination of the optical isomers.

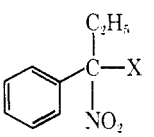
The lactam I has been obtained by heating the lactone II with ammonia[1] and from the amino ester which readily cyclizes.[2] Since neither route involves intermediates suitable for resolution, 4-nitro-4-phenylhexanoic acid (IIIa) was selected as being suitable for both resolution and conversion to the lactam I. These expectations have been realized.



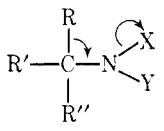
I



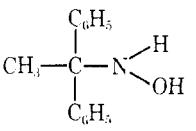
II



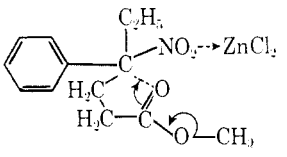
IIIa, X = $CH_2CH_2CO_2H$
b, X = $CH_2CH_2CO_2CH_3$
c, X = H



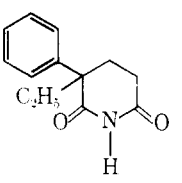
IV



V



VI



VII

1-Bromo-1-phenylpropane was converted to 1-nitro-1-phenylpropane (IIIc) most easily in dimethyl sulfoxide[3,4] rather than in N,N-dimethylformamide, although a considerable amount of propiophenone was formed in large-scale experiments.[5] The nitro compound IIIc added methyl acrylate smoothly in the Michael reaction, partial hydrolysis of the crude ester IIIb conveniently giving a mixture of the acid IIIa and unreacted ester IIIb, both of which were required for subsequent experiments. The nitro acid IIIa formed a beautifully crystalline salt with cinchonidine. Four recrystallizations completed the purification of the salt of the (+)-acid.[6] The progress of the resolution was followed most conveniently by decomposing samples of the salt with hydrochloric acid and measuring the rotation of the nitro acid. Partially resolved acid could not be purified by crystallization.

Before the resolution of the nitro acid IIIa was attempted, reduction of both the acid IIIa and the ester IIIb was examined using a variety of reagents. Hydrogenation of the acid or ester over palladium or platinum catalysts not surprisingly[7] led to removal of the nitrogen with formation of 4-phenylhexanoic acid or its methyl ester, respectively. Interestingly, hydrogen was not absorbed in ethyl acetate in the absence of methyl or ethyl alcohol with palladized charcoal as catalyst. Hydrogenation over noble metal catalysts in acetic acid containing anhydride and a trace of a strong mineral acid gave no lactam and less than 1% of what was probably acetamido compound.

Experiments with chemical reducing agents yielded more complex products. Stannous chloride in hydrochloric acid gave traces of the lactone II but stannous chloride–hydrogen chloride in acetic acid–acetic anhydride[8] gave, in addition, a poor but reproducible yield of the lactam I. Titanous chloride in hydrochloric acid gave 3-benzoylpropionic acid (60%) accompanied by the lactone II (1–3%) and propiophenone (3–5%). Commercial titanous chloride reagent contains zinc chloride and a second experiment established that zinc chloride–hydrochloric acid slowly converted the nitro

(1) G. Garvajal, M. Russek, R. Tapia, and G. Massieu, *Biochem. Pharmacol.*, **13**, 1059 (1964).
(2) W. Taub, to be published.
(3) D. E. Hardies, N. Kornblum and J. W. Powers, U. S. Patent 3,014,972 (Dec. 26, 1961).
(4) N. Kornblum and J. W. Powers, *J. Org. Chem.*, **22**, 455 (1957).
(5) N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. O. Larson, O. Levand, and W. M. Weaver, *J. Am. Chem. Soc.*, **79**, 6562 (1957).
(6) The ease with which the nitro acid IIIa is resolved suggests that it may be useful as a resolving agent for amines.
(7) W. H. Hartung and R. Simonoff, *Org. Reactions*, **7**, 263 (1953).
(8) A. Albert and W. H. Linnell, *J. Chem. Soc.*, 1614 (1936).

ester IIIb to the lactone II, ketonic products being absent. The nitro ester IIIb was hydrolyzed by boiling hydrochloric acid to the nitro acid IIIa, which was stable to this reagent. These facts prove that titanous chloride is essential for formation of the ketonic products and that the lactone II is formed in a separate reaction. Other chemical reducing agents are mentioned in the Experimental Section.

The formation of 3-benzoylpropionic acid and propiophenone involves breaking a C–C bond and is most easily explained in terms of migration of one substituent to nitrogen. The Stieglitz rearrangement[9] (IV) of hydroxylamines is the only reaction which accounts satisfactorily for the observed facts, and it is consistent with the known easy formation of hydroxylamines[10] by reduction of aliphatic nitro compounds. The predicted by-products, ethylamine and 3-aminopropionic acid, were not found. The formation of 3-benzoylpropionic acid and propiophenone requires alkyl rather than aryl migration, which has also been observed with N-methyldiphenylmethylhydroxylamine (V).[11] Similar rearrangements have been observed accompanying the reduction of nitrocycloalkanes with lithium aluminum hydride,[12,13] and hydroxylamines have been shown to be intermediates. In the present work, the products of the titanous chloride reduction are not accounted for by the Nef reaction[14] or by the action of strong mineral acid,[15] neither can they be explained by rearrangement of the nitro group to nitrite, *cf.* diphenylnitroacetonitrile.[16]

As a check of the above hypothesis, the reduction of 2-methyl-2-nitropropane[17] with titanous chloride was investigated and shown to give acetone and its condensation product mesityl oxide, isolated as their 2,4-dinitrophenylhydrazones. An intended investigation of 1-nitro-1-phenylcyclopentane, designed to throw light on the fate of the nitrogen, has been thwarted by the failure to oxidize[17] 1-phenylcyclopentylamine to the nitro compound.

The formation of the lactone II is shown in VI but without reference to the timing of the bond-breaking and -making processes. The C–N bond is weakened by coordination of the nitro group with a Lewis acid (*cf.* nitrobenzene and aluminum chloride[18]) and the lactone ring formed by attack on the ester group. These processes have obvious analogies with electrophilically assisted Sn1 reactions of alkyl halides[19] and with the formation of halolactones from unsaturated acids and esters.[20]

The preparation of the lactam I was finally completed by hydrogenation of the ester (IIIb) over Raney nickel (*cf.* 2-nitro-2-phenylpropane-1,3-diol[21]) and subsequent heating to effect lactamization. Esterification of the (+)-acid with diazomethane followed by hydrogenation gave the (−)-lactam in 71% yield.

The (−)-lactam I did not differ significantly in activity from the racemate, as shown in Table I.[22] Consequently the preparation of the (+)-isomer was not attempted. Our results parallel those found for α-ethyl-α-phenylglutarimide (VII).[23] Both the lactam (I)[1,2] and glutarimide (VII)[23] have been considered antagonists of γ-aminobutyric acid in the brain.[24] The low degree of stereochemical specificity shown by both I and VII may be a reflection of the absence of an asymmetric center in γ-aminobutyric acid and consequent lack of stereospecificity at the active site.

TABLE I

PHARMACOLOGY OF (±)- AND (−)-5-ETHYL-5-PHENYL-2-PYRROLIDINONE (I) IN THE MOUSE

	7-day acute toxicity LD_{50}, mg./kg. *p.o.*	ED_{50}, mg./kg. *p.o.*				
Compd.		Hexobarbital potentiation	Mouse rage	Maximal electroshock seizure	Maximal pentamethylenetetrazole seizure	Antistrychnine activity
(−)-I	536	200	107	23	41	81
(±)-I	812	155	93	27	27	47

Experimental Section[25]

1-Bromo-1-phenylpropane.—Phosphorus tribromide (392 g., 1.45 moles) was added slowly to a stirred solution of 1-phenyl-1-propanol (538 g., 3.96 moles) (prepared in 98% yield by reducing propiophenone with ethereal lithium aluminum hydride), in dry benzene (1 l.), moderating the reaction by cooling with an ice bath. The reaction was completed by boiling under reflux for 30 min. After cooling, the upper layer was removed, washed successively with $NaHCO_3$ solution and water, and dried (K_2CO_3). Distillation gave the pure bromide (719 g., 91%), b.p. 96–97° (13 mm.), $n^{24}D$ 1.5870, showing a single peak on gas–liquid partition chromatography. Bromination with HBr and acetic acid gave only fair yields of a mixture of products.

1-Nitro-1-phenylpropane.—1-Bromo-1-phenylpropane (266 g., 1.33 moles) was added slowly to a stirred solution of $NaNO_2$ (156 g., 2.26 moles) and urea (237 g., 8 moles) in dimethyl sulfoxide (960 ml.), maintaining the temperature at 10–12°. After a further 2 hr. at 10–12°, the dark green solution was poured into ice water (3 l.). The products from three preparations were combined and extracted several times with hexane. The dried ($MgSO_4$) extracts were distilled, and the nitro compound (457 g., 68.8%) was collected at 80–84° (0.4 mm.), $n^{22}D$ 1.5135.

Anal. Calcd. for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.44. Found: C, 65.63; H, 6.92; N, 8.55.

The infrared spectrum of a thin film showed bands at 1548 and 1370 $cm.^{-1}$, associated with the NO_2 group.

4-Nitro-4-phenylhexanoic Acid and the Methyl Ester.—The nitro compound (470 g., 2.85 moles) was dissolved in anhydrous methanol (1760 ml.) containing sodium methoxide (from 8.55 g. of sodium, 0.37 g.-atom), and methyl acrylate (684 g.,

(9) C. W. Porter, "Molecular Rearrangements," Chemical Catalog Co., Reinhold Publishing Corp., New York, N. Y., 1928, pp. 30–34, and references therein.

(10) H. B. Hassard and E. F. Riley, *Chem. Rev.*, **32**, 373 (1943).

(11) M. E. Maven, Thesis, University of Chicago, 1928; *Chem. Abstr.*, **22**, 3639 (1928).

(12) G. E. Lee, E. Lunt, W. R. Wragg, and H. J. Barber, *Chem. Ind.* (London), 417 (1958).

(13) H. J. Barber and E. Lunt, *J. Chem. Soc.*, 1187 (1960).

(14) W. E. Noland, *Chem. Rev.*, **55**, 137 (1955).

(15) V. Meyer and C. Wurster, *Ber.*, **6**, 1168 (1873).

(16) H. A. Rolewicz, *Chem. Ind.* (London), 1389 (1957).

(17) N. Kornblum, R. J. Clutter, and W. J. Jones, *J. Am. Chem. Soc.*, **78**, 4003 (1956).

(18) R. E. Van Dyke and H. E. Crawford, *ibid.*, **73**, 2018 (1951).

(19) A. Streitweiser, "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962.

(20) P. M. G. Bavin, *Can. J. Chem.*, **39**, 2035 (1961), and references therein.

(21) P. M. Ruoff and J. R. Miller, *J. Am. Chem. Soc.*, **72**, 1417 (1950).

(22) B. E. Everitt, G. H. Hall, and E. M. Taylor, *Brit. J. Pharmacol.*, in press.

(23) R. Branchini, G. Casini, M. Ferappi, and S. Galinelli, *Farmaco* (Pavia), *Ed. Sci.*, **15**, 734 (1960).

(24) F. Leonard, A. Wajngunt, M. Klein, and H. Meyer, *J. Med. Chem.*, **6**, 539 (1963).

(25) Melting points were recorded using an Electrothermal apparatus consisting of a gas-heated block equipped with a thermometer calibrated for stem exposure. Microanalyses were carried out by Mr. M. Graham. Rotations were measured for solutions in chloroform using a Bendix Ericson recording polarimeter, Type 143-A. The identities of samples were established by comparing as may of the following as were appropriate: melting point, infrared spectra, behavior on thin layer chromatography, and retention temperatures for programmed gas-liquid partition chromatography.

8 moles) was added slowly with stirring while maintaining the temperature at 20° with an ice bath. After 4 days at 20–24°, a solution of KOH (256 g., 4.5 moles) in water (300 ml.) was added and the mixture refluxed for 2 hr. Methanol was removed by distillation under reduced pressure and the residue was diluted with an equal volume of water.

Methyl 4-nitro-4-phenylhexanoate was extracted into ether–hexane (4:1). The dried (K_2CO_3) extracts were shaken with charcoal, filtered, and concentrated to give the ester as colorless prisms (175 g., 24.5%), m.p. 61–64°, raised to 64–65° by a recrystallization.

Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.13; H, 6.82; N, 5.58. Found: C, 62.30; H, 6.78; N, 5.69.

The crude **nitro acid** obtained by acidification of the aqueous liquor was dissolved in $NaHCO_3$ solution, shaken with charcoal, filtered, and reprecipitated with HCl. Crystallization from ether–hexane gave colorless prisms (313 g., 46.4%), m.p. 112–116°, raised to 116–117° by a further crystallization.

Anal. Calcd. for $C_{12}H_{15}NO_4$: C, 60.74; H, 6.37; N, 5.91; equiv. wt., 237.3. Found: C, 60.78; H, 6.37; N, 5.70; equiv. wt., 240.0.

(+)-4-Nitro-4-phenylhexanoic Acid.—Cinchonidine (98.5 g., 0.33 mole) and the nitro acid (79.5 g., 0.33 mole) were dissolved in the minimum of hot ethanol. **Cinchonidine 4-nitro-4-phenylhexanoate** (69 g.) crystallized on cooling as long white needles, m.p. 147–148°.

Anal. Calcd. for $C_{31}H_{37}N_3O_5 \cdot H_2O$[26]: C, 67.74; H, 7.15; N, 7.65. Found: C, 68.14, 67.84; H, 7.02, 6.99; N, 7.67.

The acid, generated by shaking the salt with ether and dilute HCl, showed $[\alpha]^{22}D$ +14.6°, not increased by crystallization from benzene. The cinchonidine salt was recrystallized from ethanol five times and the progress of the resolution was followed by measuring $[\alpha]D$ for the acid rather than the sparingly soluble salt. The rotation was unchanged by the last two recrystallizations, giving for pure **(+)-nitro acid**, $[\alpha]^{22}D$ +23.4° (12.1 g., 62%).

Found: C, 61.24; 61.06; H, 6.42; 6.44; N, 5.73.

Cinchonidine (+)-4-nitro-4-phenylhexanoate showed $[\alpha]^{22}D$ +55.6° in ethanol.

(−)-5-Ethyl-5-phenyl-2-pyrrolidinone.—The pure (+)-acid (12.1 g.) was esterified with ethereal diazomethane, giving the (+)-methyl ester, m.p. 77.5–79°, $[\alpha]^{22}D$ +20.7°. A solution of the (+)-ester in ethanol (40 ml.) was hydrogenated at 70° and 20 atm. for 8 hr., using 1 g. of Raney nickel as catalyst.[27] These conditions are optimal. After removing the catalyst by filtration, the filtrate was evaporated and the residue[28] was heated on the steam bath for 2 hr. Crystallization from benzene–hexane gave the (−)-lactam (6.9 g., 71%) as colorless prisms, m.p. 121.5–123.0°, $[\alpha]^{22}D$ −114°.

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 75.98; H, 8.11; N, 7.29.

Under similar conditions the racemic ester gave racemic lactam (74%), m.p. 114.5–116°, identical with a sample provided by Professor Taub.

Found: C, 76.01; H, 8.20; N, 7.35.

4-Phenylhexanoic Acid.—The nitro acid (2 g.) was hydrogenated in ethanol (15 ml.) at atmospheric pressure, using 10% palladized charcoal (0.1 g.). The uptake of hydrogen was complete in 90 min. After removing the catalyst by filtration, the filtrate was evaporated, diluted with HCl and extracted with ether–hexane. Distillation of the extracts gave the acid (1.1 g.) as a colorless oil, b.p. 118° (0.05 mm.), $n^{25}D$ 1.5090.

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39; equiv. wt., 192.3. Found: C, 75.02; H, 8.28; equiv. wt., 196.

Cyclohexylammonium 4-phenylhexanoate crystallized from ethanol–ether as pale yellow prisms, m.p. 128–130°.

Anal. Calcd. for $C_{18}H_{33}NO_2$: C, 74.18; H, 10.03; N, 4.81. Found: C, 74.34; H, 10.06; N, 4.77.

Methyl 4-phenylhexanoate, prepared by similar reduction of the nitro ester, had b.p. 95° (0.01 mm.), $n^{24}D$ 1.4920.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.70; H, 8.79; Found: C, 75.54; H, 8.61.

Saponification gave the above acid.

Reductions with Stannous Chloride.—The nitro ester (11 g.) was dissolved in the stannous chloride–HCl–acetic acid–acetic anhydride reagent[19] (125 ml.) and the solution was maintained at 0° for 2 days. After 2 days more at room temperature, the pH of the mixture was adjusted to 7 by the addition of Na_2CO_3. After shaking vigorously with ether, the mixture was filtered to remove the solid precipitate. The ether was separated, dried ($MgSO_4$), and distilled to give an oil (1 g.), b.p. 110–120° (0.01 mm.). Gas–liquid partition chromatography on a 6-ft. silicone gum rubber column programmed from 100–300° showed two major products to be present; retention temperature 192° (70%), identical with 4-ethyl-4-phenyl-γ-butyrolactone as shown by comparison of infrared spectra; retention temperature 215° (10%), identical with 5-ethyl-5-phenylpyrrolidone. Crystallization of the distilled oil from benzene–hexane gave the lactam as colorless crystals (0.09 g., 2%), m.p. 114–116°, identical with an authentic specimen.

In other experiments, tin salts were removed by precipitation with H_2S. Despite continuous extraction with ether or chloroform at pH 2, 7, and 10, other products were not isolated. Reductions carried out with stannous chloride–HCl in ethanol gave a very low yield (1%) of the lactone as the only isolable product.

The following reducing systems gave, at best, only traces of products with the nitro acid or ester: $Fe(OH)_2$, zinc dust and $CaCl_2$ in ethanol, hydrazine and palladized charcoal, H_2S and ammonia in ethanol, Na_2S, NaHS, and $NaHCO_3$ in methanol.[29]

4-Ethyl-4-phenyl-α-butyrolactone.—The lactone, prepared from propiophenone by the Stobbe condensation,[30] had b.p. 114–118° (0.1 mm.), $n^{20}D$ 1.5298 (lit.[30] $n^{23}D$ 1.5283).

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42; Found: C, 75.87, 75.87; H, 7.77, 7.48.

Gas–liquid partition chromatograms showed only one peak.

Reductions with Titanous Chloride.—Following trial experiments, the nitro ester (18.3 g.) in ethanol (70 ml.) was boiled under reflux for 30 min. with titanous chloride reagent (550 g., 15% w./v.) and concentrated HCl (550 g.), made up to 8 l. with hot water. After cooling, the mixture was extracted several times with ether. The extracts were washed with Na_2CO_3 solution, dried (K_2CO_3), and distilled to give an oil (3.2 g.). Gas–liquid partition chromatograms showed the presence of propiophenone and 4-ethyl-4-phenyl-γ-butyrolactone corresponding to yields of 3.5 and 1.3%, respectively. The presence of propiophenone was confirmed by preparing the 2,4-dinitrophenylhydrazone, m.p. and m.m.p. 194–196°, after chromatography on alumina. The lactone was not purified by microdistillation, but a pure sample was prepared by preparative gas–liquid partition chromatography and the identity was established by comparing infrared spectra.

The Na_2CO_3 extracts were shaken with charcoal, filtered, and poured into excess HCl. Extraction with ether and evaporation of the extracts gave 3-benzoylpropionic acid (8.8 g., 60%), m.p. 118–120°, identical with an authentic specimen. Ethyl 3-benzoylpropionate, prepared by esterifying the acid with ethanolic HCl, was not detected by gas–liquid partition chromatography in the above-mentioned oil.

Reduction of 2-Methyl-2-nitropropane.—A solution of 2-methyl-2-nitropropane[17] (2 g.) in ethanol (20 ml.) was boiled under reflux for 10 min. with 14% titanous chloride solution (66 g.) and concentrated HCl (66 ml.) diluted to 1 l. with water. The mixture was steam distilled into Brady's reagent and the precipitated 2,4-dinitrophenylhydrazones were collected and dried. Column chromatography on alumina using hexane and increasing proportions of ether as eluent gave acetone 2,4-dinitrophenylhydrazone, m.p. and m.m.p. 124–126°. Thin layer chromatograms confirmed the identity and showed the presence of smaller amounts of mesityl oxide 2,4-dinitrophenylhydrazone.

1-Phenylcyclopentylamine.—1-Phenylcyclopentanecarboxylic acid[31] was converted to the acid chloride with thionyl chloride and this chloride was purified by distillation. **1-Phenylcyclopentanecarboxamide** separated from heptane as colorless needles, m.p. 111–112°.

Anal. Calcd. for $C_{12}H_{15}NO$: N, 7.40. Found: N, 7.54.

A solution of the acid chloride (50 g.) in anhydrous toluene (50 ml.) was added to a stirred suspension of sodium azide (27 g.) in anhydrous toluene (300 ml.) maintained at 80°. The mixture was boiled under reflux for 4 hr., cooled, and filtered, and the

(26) Several other salts of cinchonidine are hydrated.

(27) British Drug Houses stabilized catalyst.

(28) The residue could not be recrystallized and was probably the amino ester.

(29) H. H. Hodgson and E. R. Ward, *J. Chem. Soc.*, 242 (1948).

(30) W. S. Johnson, J. W. Peterson, and W. P. Schneider, *J. Am. Chem. Soc.*, **69**, 74 (1947).

(31) C. H. Tilford, M. G. Van Campen, and J. S. Shelton, *ibid.*, **69**, 2901 (1947).

filtrate was evaporated under pressure. The residue was at once refluxed for 2 hr. with concentrated HCl (180 ml.) and water (180 ml.). After cooling, recovered acid (30 g.) was removed by filtration and the filtrate was basified and extracted with ether. Evaporation of the ether left the **amine** as an oil, the **hydrochloride** (12 g.) separating from 2-propanol–ether as colorless needles, m.p. 228–229°.

Anal. Calcd. for $C_{11}H_{15}N\cdot HCl$: C, 66.82; H, 8.16; N, 7.09. Found: C, 66.97; H, 8.07; N, 7.20.

Several attempts to oxidize the amine as described for *t*-butylamine[17] failed to give identifiable products.

Acknowledgments.—The author is indebted to C. S. Whyatt and A. Davey for technical assistance and to G. H. Hall for pharmacological results. D. W. Hills (Smith Kline and French Research Institute) measured the optical rotations. The author is particularly indebted to Professor William Taub of the Weizmann Institute, Rehovoth, Israel, and to Dr. R. G. W. Spickett, late of these laboratories, for their generous encouragement and interest.

9-Deamidooxytocin, an Analog of the Hormone Containing a Glycine Residue in Place of the Glycinamide Residue[1]

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The synthesis of 9-deamidooxytocin, in which the glycinamide residue at position 9 in oxytocin has been replaced by a glycine residue, is described. The synthetic intermediate of this analog was the protected nonapeptide benzyl ester, benzyl N-carbobenzoxy-S-benzyl-L-cysteinyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-L-leucylglycinate. From it the reduced form of the analog was prepared by the action of sodium in liquid ammonia, and the analog itself was subsequently obtained by oxidative cyclization. The biological properties of the compound, in terms of the pharmacological activities exhibited by oxytocin, have been determined and are reported.

The present communication reports the synthesis of 9-deamidooxytocin, an analog of oxytocin in which the glycinamide residue in the terminal position of the side chain of the molecule has been replaced by that of glycine, and includes the comparison of various biological activities of this analog with the hormone itself, the structure of which is shown in Figure 1. In a previous communication such a comparison was made between the pharmacological behavior of the analog in which the glutamine residue at position 4 was replaced by that of glutamic acid.[2] This 4-deamidooxytocin (4-glutamic acid oxytocin) was found to possess approximately 1/1000 of the avian depressor, 1/300 of the oxytocic, and 1/50 of the milk-ejecting activities of oxytocin. Thus, these activities, characteristic of oxytocin, were drastically reduced by replacement of the carboxamide group at position 4 by a carboxyl group, and we therefore became interested in determining whether replacement of a carboxamide group by a carboxyl at position 9 would have a comparable effect.

For the synthesis of 9-deamidooxytocin, a protected nonapeptide benzyl ester intermediate was synthesized, the benzyl ester function being at the position where the free carboxyl group was ultimately desired. Treatment of the protected nonapeptide ester with sodium in liquid ammonia by the method of Sifferd and du Vigneaud,[3] as used in the synthesis of oxytocin,[4] cleaved the protecting benzyl groups from the cysteine sulfhydryl groups and the carbobenzoxy group from the 1-cysteine amino group, and at the same time cleaved the benzyl ester to liberate the free carboxylic acid. The analog itself was obtained by subsequent oxidation and was purified by countercurrent distribution. The protected nonapeptide ester, benzyl N-carbobenzoxy-S-benzyl-L-cysteinyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-L-leucylglycinate, was prepared by a dicyclohexylcarbodiimide coupling[5] of the protected pentapeptide, N-carbobenzoxy-S-benzyl-L-cysteinyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparagine,[6] and the tetrapeptide benzyl ester, benzyl S-benzyl-L-cysteinyl-L-prolyl-L-leucylglycinate. The latter compound was obtained by a sequence of reactions starting with the coupling, by the mixed-anhydride method,[7] of N-carbobenzoxy-L-prolyl-L-leucine[8] and benzyl glycinate[9] to give benzyl N-carbobenzoxy-L-prolyl-L-leucylglycinate. Hydrogen bromide in acetic acid was used to remove the carbobenzoxy group from this protected tripeptide and the resultant product was coupled with N-carbobenzoxy-S-benzyl-L-cysteine[10] to give benzyl N-carbobenzoxy-S-benzyl-L-cysteinyl-L-prolyl-L-leucylglycinate, from which the carbobenzoxy group was removed by hydrogen bromide in acetic acid.

The protecting groups were removed from the protected nonapeptide ester by the action of sodium in liquid ammonia, and oxidative ring closure was accomplished by aeration[4] followed by treatment with aqueous potassium ferricyanide solution.[11] The ferrocyanide and excess ferricyanide ions were removed

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(2) I. Photaki and V. du Vigneaud, *J. Am. Chem. Soc.*, **87**, 908 (1965).

(3) R. H. Sifferd and V. du Vigneaud, *J. Biol. Chem.*, **108**, 753 (1935).

(4) V. du Vigneaud, C. Ressler, J. M. Swan, C. W. Roberts, P. G. Katsoyannis, and S. Gordon, *J. Am. Chem. Soc.*, **75**, 4879 (1953); V. du Vigneaud, C. Ressler, J. M. Swan, C. W. Roberts, and P. G. Katsoyannis, *ibid.*, **76**, 3115 (1954).

(5) J. C. Sheehan and G. P. Hess, *ibid.*, **77**, 1067 (1955).

(6) M. Bodanszky and V. du Vigneaud, *ibid.*, **81**, 2504 (1959).

(7) J. R. Vaughan, Jr., and J. A. Eichler, *ibid.*, **75**, 5556 (1953).

(8) W. D. Cash, *J. Org. Chem.*, **26**, 2136 (1961).

(9) L. Zervas, M. Winitz, and J. P. Greenstein, *ibid.*, **22**, 1515 (1957).

(10) C. R. Harington and T. H. Mead, *Biochem. J.*, **30**, 1598 (1936); B. Hegedüs, *Helv. Chim. Acta*, **31**, 737 (1948).

(11) V. du Vigneaud, G. Winestock, V. V. S. Murti, D. B. Hope, and R. D. Kimbrough, Jr., *J. Biol. Chem.*, **235**, PC 64 (1960); D. B. Hope, V. V. S. Murti, and V. du Vigneaud, *ibid.*, **237**, 1563 (1962).