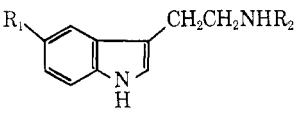
TABLE II



No.	R_1	R_2	Spontaneous activity[a] Accum counts (mean ± S.D.)	% decrease	$p<$
1[b]	H	C_6H_5CO	531 ± 73		NS
2	H	$C_{10}H_7CO$	500 ± 98		NS
3[b]	H	$C_6H_5CH_2CO$	310 ± 53	38.6	0.01
4[c]	H	$3,4\text{-}Cl_2C_6H_3CO$	462 ± 57	16.2	0.05
5[c]	Br	$3,4\text{-}Cl_2C_6H_3CO$	158 ± 73	64.5	0.001
6	H	C_6H_5NHCO	544 ± 45		NS
7	H	$3\text{-}ClC_6H_4NHCO$	443 ± 126		NS
8	H	$4\text{-}ClC_6H_4NHCO$	462 ± 63	15.3	0.1
9	H	$3,4\text{-}Cl_2C_6H_3NHCO$	613 ± 95		NS
10[b]	H	$C_6H_5SO_2$	488 ± 99		NS
11	H	$3\text{-}NO_2C_6H_4SO_2$	608 ± 40		NS
12	H	$3\text{-}NH_2C_6H_4SO_2$	648 ± 50		NS
13	H	$C_6H_5CH{=}CHSO_2$	362 ± 129	29.0	0.1

[a] See Experimental Section. [b] For synthesis, see B. T. Ho, W. M. McIsaac, L. W. Tansey, and P. M. Kralik, *J. Pharm. Sci.*, **57**, 1998 (1968). [c] For synthesis, see B. T. Ho, W. M. McIsaac, and L. W. Tansey, *ibid.*, **58**, 563 (1969).

portions), H_2O (100-ml), satd $NaHCO_3$ (two 100-ml portions), and again H_2O (100 ml). The CH_2Cl_2 phase was dried (Na_2SO_4) and then evapd *in vacuo* to yield 11.5 g (83%) of product, mp 102–103°. Recrystn from EtOH gave 10.2 g (74%), mp 101–102°. *Anal.* ($C_{16}H_{15}N_3O_4S$) C, H, N.

N-β-3-Indolylethyl-*m*-aminobenzenesulfonamide (12).—A suspension of 9.2 g (27 mmoles) of N-β-3-indolylethyl *m*-nitrobenzenesulfonamide (**11**) and 0.5 g of 10% Pd/C in 150 ml of EtOH was shaken with H_2 at 2–3 atm until the absorption ceased (about 1 hr). The filtered EtOH soln was evapd *in vacuo* to yield 7.9 g (94%) of product, mp 117–118°. Recrystn from EtOH gave 6.7 g (80%), mp 118–119°. *Anal.* ($C_{16}H_{17}N_3O_2S$) C, H, N.

N-β-3-Indolylethyl-2-naphthamide (2).—In a similar manner as described for the prepn of **11**, tryptamine (I) in $CHCl_3$ was treated with $C_{10}H_7COCl$ in the presence of Et_3N. After stirring at ambient temp for 15 hr, a solid product was filtered and washed first with H_2O then with Et_2O; yield, 3.8 g (80%), mp 188–191.5°. Recrystn from $C_6H_5CH_3$ gave 3.0 g (63%), mp 192–194°. *Anal.* ($C_{21}H_{18}N_2O$) C, H, N.

N-β-3-Indolylethyl-styrylsulfonamide (13).—To a chilled soln of 0.8 g (5 mmoles) of tryptamine (I) and 1.0 ml (12.4 mmoles) of pyridine in 15 ml of $CHCl_3$ was added slowly 1.0 g (5 mmoles) of β-styrenesulfonyl chloride. A green ppt formed instantly and changed to bright yellow in a few min. After the mixt was stirred at room temp for 15 hr, 330 mg (34%) of tryptamine·HCl was removed by filtration. The $CHCl_3$ filtrate was washed successively with 10-ml portions of H_2O, 2 N HCl, 2 N NaOH, and again H_2O, dried (Na_2SO_4), treated with charcoal, filtered, and then evapd *in vacuo*. The oily residue was dissolved in C_6H_6, and petr ether was added to cloudiness. Chilling of the mixt caused the sedimentation of a pale yellow solid together with a yellow oil. The oily product was sepd by decantn and dissolved in a small amount of petr ether. Crystn took place on chilling to yield 350 mg (22%) of yellow product, mp 135–140°. Addn of more petr ether and chilling gave another 310 g (20%) of less pure product. Subsequent recrystns from MeOH afforded an anal. sample, mp 147.5–149°. *Anal.* ($C_{18}H_{18}N_2O_2S$) C, H, N.

Phenyl N-β-Indolylethylcarbamate (IV).—To a stirred suspension of 3.2 g (20 mmoles) of tryptamine (I) in a mixt of 100 ml of Et_2O and 20 ml of H_2O was added at ice temp one-half of 3.2 g (20 mmoles) of $ClCO_2C_6H_5$. The remaining half of $ClCO_2C_6H_5$ was added dropwise simultaneously with a total of 10 ml of 2 N NaOH in such a manner that the reaction temp was maintained near 5°. After stirring for an addl 45 min at ambient temp, the org layer was sepd, washed successively with 15-ml portions of 5% HCl and H_2O, dried (Na_2SO_4), treated with charcoal, and then coned *in vacuo* to about 50 ml. Petr ether was added to the Et_2O soln to cloudiness, and chilling brought down 3.5 g (64%) of pale pink plates, mp 66–69°. Three recrystns from Et_2O–petr ether gave an anal. sample as small, pale yellow crystals, mp 70–71.5°. *Anal.* ($C_{17}H_{16}N_2O_2$) C, H, N.

N-β-3-Indolylethyl-N'-4-chlorophenylurea (8).—A mixt of 1.0 g (4.05 mmoles) of phenyl N-4-chlorophenylcarbamate (IIIc), 0.57 g (4.05 mmoles) of tryptamine (I), and 30 ml of dioxane was refluxed for 2 hr. The cooled soln was poured into 50 g of ice with stirring. The white solid was collected on a filter and recrystd from 75% EtOH; yield, 1.0 g (83%) of shiny white needles, mp 196–198°. One more recrystn from 50% EtOH gave an anal. sample, mp 198–200°.

See Table II for physical constants of **6**, **7**, and **9** prepd by the same method.

Pharmacology. Effects on Spontaneous Motor Activity.—For each compd in Table I, 15 male Yale–Swiss mice (Texas Inbred Co., Houston, Texas) were used. The animals were divided into 5 groups of 3, and each animal was injected ip with 100 μmoles/kg of the compd in a Tween-80 and saline supension. (For better suspension each compd was ground before mixing.) Fifteen minutes was allowed between each group injection. After the injection, each group of 3 mice was placed inside an activity cage (Metro Scientific Co.) and counted for 10 min. To allow for the initial curiosity of animals in a new environment, counts in the first 5 min were disregarded, and those in the last 5 min were considered for an actual reading. Injections and readings were timed so that the peak time of the action of the compds (30 min postinjection) fell within the 5 min of actual reading time.

The mean and standard deviation of the scores (5-min net counts) of the 5 experimental groups and those of the 5 control groups were calcd. The values of each compd were compared with those of the controls, and treated statistically, using the Student t method. For those values that were significant, the per cent change in spontaneous motor activity was then calcd.

Determination of ED_{50}.—Ten mice were injected ip with a minimum of 6 doses of **3** and **5** in a Tween-80 and saline suspension; 10 control mice were given only the vehicles. Animals were run in the activity cage individually for a total of 10 min. Since the first 6 min was regarded as a stage of curiosity, only the counts in the last 4 min were considered for an actual reading.

Each score (4-min net counts) of individually run, experimental animals was compared to the mean and standard deviation of the scores of the control animals. Those scores of experimental animals falling outside of the range of the control standard deviation were considered to be significant. ED_{50} was determined by plotting dose *vs.* per cent of animals affected by the compd at a given dose (method of Miller and Tainter[4]).

Acknowledgment.—The authors wish to thank Miss Karen Kelly for her technical assistance.

(4) L. D. Miller and M. L. Tainter, *Proc. Soc. Exp. Biol. Med.*, **57**, 261 (1944).

Quinuclidine Analogs of Tobacco Alkaloids

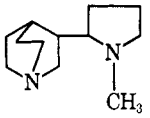
F. D. REED AND ALFRED BURGER*

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901

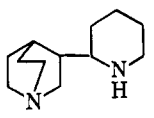
Received December 23, 1970

Since quinuclidine possesses a tertiary amino N in a rigid nonplanar ring system and is present in many biologically active alkaloids[1,2] and other compounds,[3] it was of interest to investigate changes in pharmacologic activity that result from the substitution of a 3-quinuclidinyl group for the planar 3-pyridyl moiety of nicotine and anabasine. This note describes the synthesis and pharmacologic evaluation of 3-(1-methyl-2-pyrrolidinyl)- (**1**) and 3-(2-piperidinyl)quinuclidine (**2**).

(1) R. B. Turner and R. B. Woodward, *Alkaloids*, **3**, 1 (1950).
(2) W. I. Taylor, *ibid.*, **11**, 73 (1968).
(3) M. D. Mashkovsky and L. N. Yakhontov, *Fortschr. Arzneimittelforsch.*, **13**, 293 (1969).



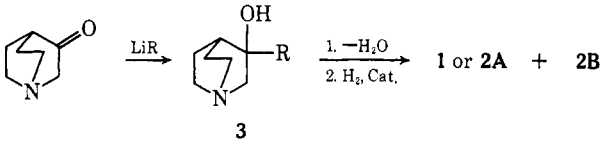
1



2

The syntheses were carried out by condensing 1-methyl-2-pyrryllithium and 2-pyridyllithium, resp, with 3-quinuclidinone, dehydrating the resulting tertiary alcohols, and saturating the resulting unsaturated compounds by catalytic hydrogenation. In the case of **2**, two diastereomers could be separated by fractionation of the diliturate salts. From an inspection of Godfrey molecular models, the only sterically unrestricted isomers can be (Quin)e–(Pip)e, and (Quin)a–(Pip)e.

A nicotine analog in which the pyrrolidine moiety had been replaced by 2-quinuclidinyl has been described previously without biological data.[4]



3

3a, R = 1-methyl-2-pyrryl
3b, R = 2-pyridyl

Pharmacology.—Compounds **1, 2** (both stereoisomers), and **3b** were evaluated by Dr. G. E. Groblewski, Mr. G. C. Zirzow, and Miss Mary Coan at Woodard Research Laboratories, Herndon, Va. In the dog, **1**·ditartrate caused dose-dependent hypotensive responses which were not due to stimulation of muscarinic receptors. Cholinolytic and antihistaminic actions were also observed. The compound displayed a preferential parasympathetic ganglionic blocking activity.

The pharmacologic profiles of **3b**, **2A**, and **2B** in the anesthetized dog did not resemble that of nicotine (hypertension, stimulation of rate and depth of respiration, tachycardia). All three compounds produced hypotension and affected heart rate and respiration moderately or not at all. The tertiary alcohol **3b** exhibited differential ganglionic blocking actions, cholinolysis, and adrenolysis. A high dose (32 mg/kg) blocked the stimulant action of nicotine on respiration.

Stereomer **2A** blocked the effects of vagal stimulation (cholinergic ganglia); stereomer **2B** displayed anticholinergic activity and blocked the respiratory stimulant action of nicotine.

Experimental Section

Melting points were detd with a Thomas-Hoover melting point apparatus and are uncorrected. The ir and nmr spectra of all compds were measured and were as expected. Analyses for elements indicated by the symbols of the elements were within 0.2% of the calcd values.

Pharmacology.—In the mouse, **1** had iv MED_{50} 18 mg/kg, LD_{50} 180 mg/kg (95% confidence limits); **3b**, **2A**, and **2B** had MED_{50} 10 mg/kg, LD_{50} 56 mg/kg.

In the phenobarbitalized dog, ganglionic blocking activity was observed after 10 mg/kg iv of **1**·ditartrate, expressed by vagolytic action, although a response to exogenous ACh was still observed. This indicates a blocking action on parasympathetic ganglia. After injection of atropine sulfate (0.5 mg/kg), a 50-mg dose of **1**·ditartrate caused a 48-mm drop in the blood pressure response to dimethylphenylpiperazinium iodide (DMPP). The response to norepinephrine (NE) at this time was unaffected; thus, **1** possesses both sympathetic and parasympathetic ganglionic blocking actions, the parasympathetic ganglia being blocked at low doses.

Table I
Pharmacology in the Mouse

Compd	Iv dose, mg/kg	Prominent signs
1	32–100	Increased locomotor activity, rubbing nose, irregular rate and depth of respiration
3b	10	Rubbing nose, mydriasis
	32	Decreased locomotor activity, rubbing nose, mydriasis, irregular respiratory depth and rate, motor deficits
2A	10	Rubbing nose, irregular respiratory rate
	32	As with 10 mg; irregular respiratory depth, motor deficits; tremors at rest and with movements
2B	10	As with 2a (10 mg); tremors with movements
	32	As with 2a (32 mg)

Compound **3b** (10–30 mg/kg) reduced both magnitude (−15 to −25 mm) and duration (1.7–8.3 min) of the hypotensive response after atropine (*vide supra*) in the dog. Thus, peripheral cholinergic receptors appear to be involved in the response. Also, **3b** nearly completely blocked the action of exogenous ACh on the blood pressure. After 1.0 mg/kg of **3b**, the response to vagal stimulation was blocked completely, whereas a small response to ACh was still observed.

At 30 mg/kg (total dose, 41.1 mg/kg) **3b** blocked the hypertensive action of *N*-benzyl-3-pyrrolidylacetate methobromide (NBPA, a sympathetic ganglionic nonnicotinic stimulant) even though a response to NE was observed. Atropine (dose as above), following another 30-mg/kg injection of **3b**, produced a partial block of the pressor response to DMPP. Thus, **3b** exerts a selective ganglionic blockage affecting in order (a) parasympathetic ganglia; (b) nonnicotinic receptors in sympathetic ganglia; and (c) nicotinic receptors in sympathetic ganglia.

Inhibition of the pressor effect of NE by **3b** (10 mg/kg) is difficult to explain because the blood pressure responses to NBPA, DMPP, and nicotine were unaffected.

Similar experiments with diastereoisomers **2A** and **2B** proved that **2B** was the more potent hypotensive agent. The hypotensive action was not blocked by atropine in a dose which prevented response to ACh, and, therefore, could not be due to stimulation of cholinergic receptors. An anticholinergic activity of **2B** is difficult to explain because the response to vagal stimulation was unimpaired. Equally unexpected were antinicotinic actions after 1.0 mg/kg of **2B**. Since the effects of NE were uninhibited, blockade of nicotinic sites in sympathetic ganglia is indicated. However, DMPP was not blocked at this time, and the responses of blood pressure and heart rate to nicotine reverted to control values after atropine administration. The block of the stimulant action on respiration was not relieved.

The second of two 1-mg/kg injections of **2B** inhibited the carotid sinus reflex. At this time, response to NE, DMPP, and nicotine were equal to, or greater than, control values, thus eliminating the adrenergic receptor and sympathetic ganglion as the site of the blockade. The blocking action might be exerted at central synapses or at the baroreceptors.

Chemistry. 3-(1-Methyl-2-pyrryl)-3-quinuclidinol (3a).—A soln of 1-methylpyrrole (37.3 g, 0.46 mole) and *n*-BuLi (28.12 g, 0.44 mole, in hexane) in dry THF (100 ml) under N_2 was heated gradually with stirring to 55° over 3 hr until evolution of BuH ceased.[5] The mixt was cooled to −40° and 3-quinuclidinone (25 g, 0.2 mole) in 50 ml of THF was added dropwise with stirring during 25 min. The temp was allowed to rise to 25°, and stirring was continued for 5 hr. The mixt was then cooled to −20° and decompd slowly with H_2O. The org layer was sepd, the aq soln was extd exhaustively with $CHCl_3$, and the exts were combined, dried (Na_2SO_4), and evapd. The cryst residue was recrystd from Me_2CO; colorless crystals (28.5 g, 69%); mp 148–149°; they sublimed readily at 120° (1 mm). *Anal.* ($C_{12}H_{18}N_2O$) C, H; *m/e* 206.

3-(1-Methyl-2-pyrrolidinyl)quinuclidine (1).—A soln of **3a** (10 g, 50 mmoles) in DMSO (50 ml) was heated at 165° for 16 hr.[6]

(4) A. S. Sadykov, M. Karimov, and Kh. A. Aslanov, *Zh. Obshch. Khim.*, **33**, 3417 (1963).

(5) *Cf.* D. A. Shirley, B. H. Gross, and P. A. Roussel, *J. Org. Chem.*, **20**, 225 (1955).

(6) *Cf.* V. J. Traynelis, W. L. Hergenrother, J. R. Livingston, and J. A. Valicenti, *ibid.*, **27**, 2377 (1962).

Satd aq NaCl (50 ml) was added, the soln was extd with C_6H_6 (4 × 100 ml), the solvent was evapd, and the tacky residue was chromatographed (Florisil, petr ether, bp 60–100°). The viscous product weighed 7.54 g (80% yield). It was dissolved in EtOH (100 ml) and HCl (7.7 ml) and hydrogenated at 3.71 kg/cm² in the presence of 5% Rh/C (3 g) at 45° for 45 hr. Filtration from the catalyst, evapn of EtOH, addition of LiOH, extn with $CHCl_3$, and evapn of the solvent yielded oily **1**, di(5-nitrobarbiturate): yellow crystals from H_2O (5.2 g, 62%); mp 251–252°. *Anal.* ($C_{20}H_{28}N_2O_{11}\cdot H_2O$) C, H, N. The di-*d*-tartrate was prepd. in Me_2CO and crystd from MeOH, mp 161–162°. *Anal.* ($C_{20}H_{34}N_2O_6$) C, H, N. Mass spectrum of liberated oily **1** ($C_{12}H_{22}N_2$) revealed *m/e* 194.

3-(2-Pyridyl)-3-quinuclidinol (3b).—A soln of 55 g (0.35 mole) of 2-bromopyridine in 50 ml of Et_2O was added rapidly to a stirred soln of *n*-BuLi (0.35 mole) in hexane at −50° under N_2. After stirring for 20 min, a soln of 3-quinuclidinone (12.5 g, 0.1 mole) in Et_2O (100 ml) was added dropwise. The mixt was stirred for 2.5 hr while the temp was allowed to rise gradually to 25°, poured on ice–AcOH, and extd with Et_2O. The H_2O layer was made ammoniacal and extd exhaustively with $CHCl_3$. The exts were dried (Na_2SO_4) and evapd, and the residue was crystd from Me_2CO; yield 8.5 g (42%); mp 163–164°. The product sublimed at 130° (0.1 mm). *Anal.* ($C_{12}H_{16}N_2O$) C, H, *m/e* 204.

3-(2-Pyridyl)-1-azabicyclo[2.2.2]-2-octene.—An intimate mixt of **3b** (4.7 g, 23 mmoles) and powdered potassium pyrosulfate (40 g) was fused at 240° for 1 min.[7] After cooling, the melt was treated with ice, and the soln was made ammoniacal and extd exhaustively ($CHCl_3$). Evapn of the solvent and chromatography using Florisil and hexane yielded 2.87 g (64%) of colorless crystals, mp 75–76°. *Anal.* ($C_{12}H_{14}N_2$) C, H; *m/e* 186.

3-(2-Piperidinyl)quinuclidine (2).—A soln of 4.5 g (24 mmoles) of the unsatd pyridine deriv in EtOH (100 ml) and HCl (4.5 ml) was hydrogenated at 25° and 3.51 kg/cm² with PtO_2 (0.58 g) for 1.5 hr. The soln was filtered and evapd, and the residue was made basic with LiOH and extd with $CHCl_3$. The oily residue from the ext was treated with 600 ml of an EtOH soln of 5-nitrobarbituric acid (8.65 g, 0.05 mole). A ppt which formed immediately was collected, dried, and recrystd from H_2O (200 ml). Yellow rosettes (3.54 g) had mp 252–254° dec. The base was regenerated (aq KOH), extd (Et_2O), and crystd (anhyd Et_2O) at −50°: yield 1.1 g; mp 61–62° (diastereomer **2A**); tlc [Al_2O_3, $CHCl_3$–Et_2NH (5%)] R_f 0.4. *Anal.* ($C_{12}H_{22}N_2$) C, H, N; *m/e* 194.

Diastereomer 2B.—The aq mother liquor of the diliturate was concd to 50 ml and cooled to 0°. It deposited 4.86 g of yellow needles, mp 261–262° dec. The diastereoisomeric base was regenerated and recrystd as above; yield 1.7 g; mp 69–70°; tlc as above, R_f 0.6. *Anal.* ($C_{12}H_{22}N_2$) C, H, N; *m/e* 194.

Acknowledgment.—We are grateful to Philip Morris and Company, Richmond, Va., for financial support by a postdoctoral fellowship (to F. D. Reed), supplies, and defrayment of the pharmacologic investigations which made this study possible.

(7) *Cf.* F. J. Villani and C. A. Ellis, *J. Med. Chem.*, **13**, 1245 (1970).

Deamino-D-oxytocin[1]

GEORGE FLOURET AND VINCENT DU VIGNEAUD*

Department of Chemistry, Cornell University, Ithaca, New York 14850 and Department of Biochemistry, Cornell University Medical College, New York, New York 10021

Received November 19, 1970

We have previously reported[2] that the optical antipode of the posterior pituitary hormone oxytocin did not possess detectable avian vasodepressor or oxytocic activity, whereas oxytocin possesses approximately 500 units/mg of each of these activities. No indication of an inhibitory effect of D-oxytocin on these activities of oxytocin could be detected. Since deaminooxytocin is much more potent than oxytocin, it was decided to synthesize deamino-D-oxytocin and test it for these biological activities.

For the synthesis of deamino-D-oxytocin, the desired protected polypeptide amide precursor *S*-Bzl-β-mercaptopropionyl-D-Tyr-D-Ile-D-Gln-D-Asn-D-Cys(Bzl)-D-Pro-D-Leu-Gly-NH_2 (I) was prepared by the nitrophenyl ester method,[3] as employed for the synthesis of deamino-L-oxytocin,[4] starting with Z-D-Tyr(Bzl)-D-Ile-D-Gln-D-Asn-D-Cys(Bzl)-D-Pro-D-Leu-Gly-NH_2 (II).[2]

The protected polypeptide amide I was treated with Na in liquid NH_3,[5] and the resulting disulfhydryl compound was oxidized in dil aq soln with $K_3Fe(CN)_6$.[4] After removal of ferro- and ferricyanide ions with the ion-exchange resin AG3-X4 (in the Cl^- form), the soln gave a negative Ellman test.[6] The deamino-D-oxytocin thus obtd was purified by countercurrent distribution[7] or by partition chromatography[8] on Sephadex G-25 as described in the Experimental Section.

No avian vasodepressor[9] or oxytocic activity[10] was detected upon bioassay of deamino-D-oxytocin, whereas crystalline deamino-L-oxytocin possesses 975 units/mg of avian vasodepressor and 803 units/mg of oxytocic activity.[11] No indication of an inhibitory effect of deamino-D-oxytocin on the above activities of oxytocin could be detected.

Experimental Section[12]

***S*-Bzl-β-mercaptopropionyl-D-Tyr-D-Ile-D-Gln-D-Asn-D-Cys(Bzl)-D-Pro-D-Leu-Gly-NH_2 (I). Procedure A.**—A suspension of 0.6 g of II in 25 ml of F_3CCH_2OH[13] was saturated with HBr gas previously passed through towers of naphthalene and anhydrous $CaCl_2$. After 30 min the resulting soln was evapd to dryness, the residue was redissolved in F_3CCH_2OH, and the soln was evapd to dryness again. The solid residue obtained was dissolved in 40 ml of MeOH and neutralized with ion-exchange resin IRA-410 (OH). The suspension was filtered, and the filtrate, which gave a negative test for Br^- ($AgNO_3$), was evapd under vacuum and dried under vacuum over P_2O_5. A soln of 0.38 g of the free octapeptide thus obtained in 2 ml of DMF was treated with 0.17 g of *p*-nitrophenyl *S*-benzyl-β-mercaptopropionate. The waxy material formed overnight was treated with EtOH, filtered off, and washed 3 more times with EtOH; yield

* Author to whom correspondence and reprint requests should be sent at the Department of Chemistry, Cornell University, Ithaca, N. Y. 14850.

(1) This work was supported in part by Grants HE-01675 and HE-11680 from the National Heart Institute, U. S. Public Health Service.

(2) G. Flouret and V. du Vigneaud, *J. Amer. Chem. Soc.*, **87**, 3775 (1965).

(3) M. Bodanszky, *Nature (London)*, **175**, 685 (1955).

(4) 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).

(5) R. H. Sifferd and V. du Vigneaud, *ibid.*, **108**, 753 (1935).

(6) G. L. Ellman, *Arch. Biochem. Biophys.*, **82**, 70 (1959).

(7) L. C. Craig, W. Hausmann, E. H. Ahrens, Jr., and E. J. Harfenist, *Anal. Chem.*, **23**, 1236 (1951).

(8) D. Yamashiro, *Nature (London)*, **201**, 76 (1964).

(9) Avian vasodepressor assays were performed on conscious chickens according to the method of R. A. Munsick, W. H. Sawyer, and H. B. van Dyke, *Endocrinology*, **66**, 860 (1960).

(10) Oxytocic assays were performed according to the method of P. Holton, *Brit. J. Pharmacol.*, **3**, 328 (1948), as modified by R. A. Munsick, *Endocrinology*, **66**, 451 (1960), on isolated uteri from rats in natural estrus with the use of Mg-free van Dyke–Hastings solution.

(11) B. M. Ferrier, D. Jarvis, and V. du Vigneaud, *J. Biol. Chem.*, **240**, 4264 (1965).

(12) All melting points are corrected capillary melting points and were taken on a Thomas-Hoover melting point apparatus. Where analyses are indicated only by symbols of the elements, analytical results obtained for the elements were within ±0.4% of the theoretical values. All protected peptides were dried to const wt over P_2O_5 under vacuum at 100° before yields were determined.

(13) D. Yamashiro, D. Gillessen, and V. du Vigneaud, *J. Amer. Chem. Soc.*, **88**, 1310 (1966).