Journal of Medicinal Chemistry

VOLUME 9, NUMBER 2 FEBRUARY 25, 1966

Synthesis and Pharmacological Properties of 9-Decarboxamido-oxytocin[1]

LUIS A. BRANDA[2] AND VINCENT DU VIGNEAUD

Department of Biochemistry, Cornell University Medical College, New York, New York 10021

Received August 31, 1965

The intermediate for the synthesis of 9-decarboxamido-oxytocin, in which the glycinamide residue of the hormone has been replaced by that of methylamine, was the protected octapeptide methylamide, *N*-tosyl-*S*-benzyl-L-cysteinyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-*S*-benzyl-L-cysteinyl-L-prolyl-L-leucine methylamide. This compound was prepared by coupling *N*-tosyl-*S*-benzyl-L-cysteinyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparagine with *S*-benzyl-L-cysteinyl-L-prolyl-L-leucine methylamide. The *S*-benzyl-tripeptide methylamide was obtained by the removal of the carbobenzoxy group from the corresponding *N*-carbobenzoxy-*S*-benzyl-tripeptide methylamide which was the product of the coupling of *p*-nitrophenyl *N*-carbobenzoxy-*S*-benzyl-L-cysteinate and L-prolyl-L-leucine methylamide. The dipeptide methylamide was prepared by the removal of the carbobenzoxy group from the product of the coupling of *N*-carbobenzoxy-L-prolyl-L-leucine and methylamine. The protecting groups of the protected octapeptide methylamide were removed by sodium in liquid ammonia, and the resulting disulfhydryl compound was oxidatively cyclized to give the analog, which was isolated by partition chromatography on Sephadex G-25. 9-Decarboxamido-oxytocin was found to possess approximately 1/70 of the potency of oxytocin with respect to its oxytocic activity, approximately 1/100 of the potency of oxytocin with respect to its milk-ejecting activity, and was practically devoid of avian vasodepressor and rat pressor activities. It has an extremely low degree of antidiuretic activity.

The posterior pituitary polypeptide hormone, oxytocin (Figure 1), possesses oxytocic, milk-ejecting, and avian vasodepressor activities to a very high degree. It also possesses pressor and antidiuretic activities to a small degree. With the synthesis of oxytocin[3] it became possible in our own and other laboratories to undertake investigations to establish the extent to which certain features of its molecular structure determine its biological properties. As part of an extensive study of this relationship of structure to biological activity we have carried out an investigation on the importance of the amino, the phenolic hydroxyl, and the three carboxamide groups to the biological activities of oxytocin by the preparation by total synthesis of a series of analogs in which each one of these groups has been replaced by hydrogen, namely deamino-, deoxy-, 4-decarboxamido-, 5-decarboxamido-, and 9-decarboxamido-oxytocin. The effect of these replacements has been evaluated by determining the pharmacological activities of these analogs. In this way it has been possible to ascertain to what degree the chemical functional groups mentioned contribute to the aforementioned pharmacological activities of oxytocin.

In deamino-oxytocin[4] the half-cystine residue at position 1 is replaced by a β-mercaptopropionic acid residue, and in deoxy-oxytocin[5] the tyrosine residue is replaced by that of phenylalanine. 4-Decarboxamido-oxytocin[6a] contains an α-aminobutyric acid residue in place of that of glutamine, and 5-decarboxamido-oxytocin[6] contains an alanine residue in place of that of asparagine. This series of replacements of single chemical functional groups has now been completed by the synthesis reported in this communication of 9-decarboxamido-oxytocin in which the glycinamide residue at position 9 is replaced with hydrogen. This replacement is in a sense a more drastic change than the replacements of the carboxamide groups at position 4 and 5 by hydrogen which involve the replacement of one amino acid residue by another, whereas in 9-decarboxamido-oxytocin a methylamine residue replaces an amino acid residue. Nevertheless the replacement of the carboxamide group in position 9 by hydrogen offers an approach to the evaluation of the importance of the carboxamide group in this position. The results of the pharmacological study of the 9-decarboxamido-oxytocin are given in Table I which also contains the pharmacological activities of the other analogs mentioned, in which a given functional

(1) This work was supported in part by Grant HE-01675 from the National Heart Institute, U. S. Public Health Service. A preliminary report of the biological activities of 9-decarboxamido-oxytocin was presented at the International Congress of Biochemistry, New York, N. Y., July 1964.

(2) International Postdoctoral Research Fellow of the National Institutes of Health.

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

(4) (a) V. du Vigneaud, G. Winestock, V. V. S. Murti, D. B. Hope, and R. D. Kimbrough, Jr., *J. Biol. Chem.*, **235**, PC64 (1960); (b) D. B. Hope, V. V. S. Murti, and V. du Vigneaud, *ibid.*, **237**, 1563 (1962); (c) D. Jarvis and V. du Vigneaud, *Science*, **143**, 545 (1964); (d) B. M. Ferrier, D. Jarvis, and V. du Vigneaud, *J. Biol. Chem.*, **240**, 4264 (1965).

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(6) (a) V. du Vigneaud, G. S. Denning, Jr., S. Drabarek, and W. Y. Chan, *J. Biol. Chem.*, **238**, PC1560 (1963); **239**, 472 (1964); (b) S. Guttmann and R. A. Boissonnas, *Helv. Chim. Acta*, **46**, 1626 (1963).

TABLE I

BIOLOGICAL POTENCIES[a] OF OXYTOCIN AND OF EACH OF ITS ANALOGS IN WHICH ONE CHEMICAL FUNCTIONAL GROUP HAS BEEN REPLACED BY HYDROGEN

Oxytocin compd.	Vasodepressor (fowl)	Oxytocic (rat)	Milk-ejecting (rabbit)	Pressor (rat)	Antidiuretic (rat)
Oxytocin	507 ± 23[b]	546 ± 18[c]	410 ± 16[b]	3.1 ± 0.1[b]	2.7 ± 0.2[b]
Deamino-	975 ± 24[d]	803 ± 36[c,d]	541 ± 13[d]	1.44 ± 0.06[d]	~19[d]
Deoxy-	60[e]	30[e]	60[e]	~0.4[f]	~0.5[f]
4-Decarboxamido-	108 ± 5[g]	72 ± 2[c,g]	225 ± 7[h]	~0.1[g]	0.2–0.3[g]
5-Decarboxamido-	0.2–0.3[g]	0.2–0.3[c,g]	<0.05[i]	<0.01[g]	0.002[g]
9-Decarboxamido-	<0.02	7.2 ± 0.2[c]	3.8 ± 0.1	Nil[j]	~0.2

[a] Expressed in units per milligram. [b] W. Y. Chan and V. du Vigneaud, *Endocrinology*, **71**, 977 (1962). [c] This value was determined on isolated uteri from rats in natural estrus: W. Y. Chan, M. O'Connell, and S. R. Pomeroy, *Endocrinology*, **72**, 279 (1963). [d] See ref. 4d. [e] See ref 5a. [f] See ref 5d. [g] See ref 6a. [h] W. Y. Chan and V. du Vigneaud, unpublished data. [i] See ref 6b. [j] 9-Decarboxamido-oxytocin exhibited some inhibitory effect on the response to the standard in this assay.

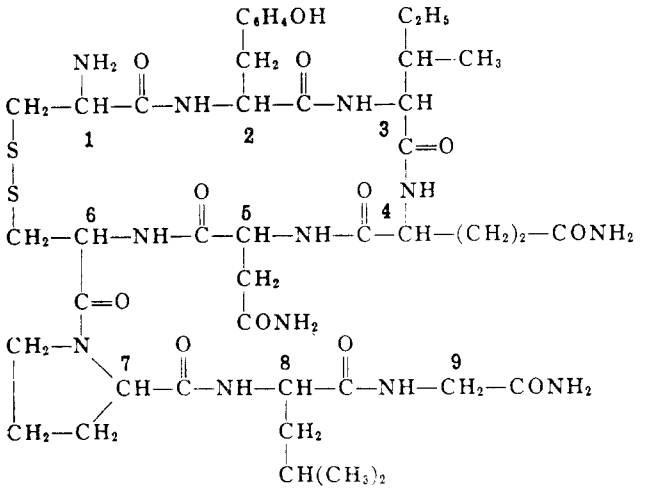

Figure 1.—Structure of oxytocin, with numbers indicating the position of the individual amino acid residues.

group is replaced by hydrogen, and includes the activities of oxytocin itself for comparison.

It can be seen from the data in Table I that the presence of the amino group at position 1 is not necessary for the possession of the biological activities which are characteristic of oxytocin, since avian vasodepressor, oxytocic, and milk-ejecting properties are exhibited by deamino-oxytocin to an even higher degree than by the parent hormone. The phenolic hydroxyl group of the tyrosine residue does not appear to be vital, but it is apparent from the activities of deoxy-oxytocin that this group does contribute to a considerable degree to the potency of oxytocin with respect to its various activities. The striking differences in the activity of 4- and 5-decarboxamido-oxytocin demonstrate that the presence of the carboxamide group of the asparagine residue at position 5 is vital for the exhibition of appreciable biological activity, whereas the presence of the carboxamide group of the glutamine residue at position 4 is not essential.

From the results of the biological assays on 9-decarboxamido-oxytocin it is apparent that the carboxamide group of the glycinamide residue plays a highly important role in the manifestation of the biological activities characteristic of oxytocin. This analog is practically devoid of avian vasodepressor activity, the activity on which the official method of assay of the U. S. Pharmacopeia for oxytocin is based. The other two characteristic activities of oxytocin, the oxytocic and the milk-ejecting activities, are only exhibited to a small degree by this analog. It might also be mentioned that when the disulfide group of oxytocin was replaced by two hydrogens, the resulting *linear* polypeptide, dethio-oxytocin, was found to possess no avian vasodepressor activity[7a] or oxytocic activity.[7b]

9-Decarboxamido-oxytocin was prepared from the protected octapeptide methylamide, *N*-tosyl-*S*-benzyl-L-cysteinyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-*S*-benzyl-L-cysteinyl-L-prolyl-L-leucine methylamide. For the preparation of this compound *N*-carbobenzoxy-L-prolyl-L-leucine methylamide was desired. It was made by coupling *N*-carbobenzoxy-L-prolyl-L-leucine[8] and methylamine by the mixed-anhydride procedure.[9] The carbobenzoxy group was then removed by hydrogenation in the presence of palladium on charcoal, and the resulting dipeptide methylamide was coupled with *p*-nitrophenyl *N*-carbobenzoxy-*S*-benzyl-L-cysteinate[10] to give the protected tripeptide methylamide, *N*-carbobenzoxy-*S*-benzyl-L-cysteinyl-L-prolyl-L-leucine methylamide. This carbobenzoxy group was cleaved by treatment with hydrogen bromide in acetic acid, and the *S*-benzyl-tripeptide methylamide so produced was then coupled, using dicyclohexylcarbodiimide as the condensing agent,[11] with the protected pentapeptide, *N*-tosyl-*S*-benzyl-L-cysteinyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparagine. This protected pentapeptide was synthesized by the method of Cash, *et al.*,[12] with minor modifications and isolated in crystalline form.

The protecting groups of the protected octapeptide methylamide so obtained were removed by treatment with sodium in liquid ammonia,[13] and the resulting disulfhydryl peptide was oxidized to the disulfide-containing analog by the action of potassium ferricyanide.[3b] The oxidized solution was deionized and 9-decarboxamido-oxytocin was isolated by partition chromatography on Sephadex G-25[14] using the solvent system water(containing 3.5% acetic acid and 1.5% pyridine)–1-butanol–benzene (8:6:1).

(7) (a) R. A. Turner, J. G. Pierce, and V. du Vigneaud, *J. Biol. Chem.*, **193**, 359 (1951); (b) Z. Beránková and F. Šorm, *Collection Czech. Chem. Commun.*, **26**, 2557 (1961).

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(12) W. D. Cash, L. McC. Mahaffey, A. S. Buck, D. E. Nettleton, Jr., C. Romas, and V. du Vigneaud, *J. Med. Pharm. Chem.*, **5**, 413 (1962).

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

(14) D. Yamashiro, *Nature*, **201**, 76 (1964).

In the biological assays carried out on 9-decarboxamido-oxytocin, four-point assay design was used. The potency of the avian vasodepressor activity was determined on conscious chickens according to the method of Munsick, Sawyer, and van Dyke.[15] Oxytocic assays were performed on isolated uteri from rats in natural estrus by the procedure of Holton,[16] as modified by Munsick.[17] Assays of the milk-ejecting activity were carried out on anesthetized rabbits by the method described by Cross and Harris,[18] as adopted by van Dyke, *et al.*,[19] and modified by Chan.[20] The rat pressor activity was measured in urethan-anesthetized male rats according to the method described in the U. S. Pharmacopeia,[21] and the antidiuretic activity was determined in hydrated male rats by the method of Jeffers, Livezey, and Austin,[22] as modified by Sawyer.[23]

Experimental Section[24]

N-Carbobenzoxy-L-prolyl-L-leucine Methylamide.—To a solution of 3.62 g of *N*-carbobenzoxy-L-prolyl-L-leucine[8] in 70 ml of peroxide-free tetrahydrofuran was added 1.50 ml of triethylamine. The solution was cooled to −10° and kept at that temperature for 5 min, then 1.40 g of isobutyl chloroformate was added, and the mixture was stirred at −10° for 20 min. A solution of 1.40 g of methylamine hydrochloride in a mixture of 4 ml of water and 3 ml of triethylamine was prepared just prior to the end of the 20-min period and was added to the reaction mixture, which was then stirred for 1.5 hr in a stoppered flask without further cooling. The tetrahydrofuran was removed by rotary evaporation until the product began to crystallize. The separation of the product was completed by the addition of 40 ml of water. After 1 hr at room temperature the crystals were collected by filtration, washed successively with a 5% solution of $KHCO_3$, H_2O, 1 *N* HCl, and H_2O, and dried (P_2O_5), giving 3.0 g, mp 127–129°. Recrystallization of this material from tetrahydrofuran–water gave a 94% yield of needles, mp 128–129°, $[\alpha]^{20}D$ −73.0° (*c* 1, ethanol). A sample dried for analysis over P_2O_5 *in vacuo* at 100° had mp 131–132°.

Anal. Calcd for $C_{20}H_{29}N_3O_4$: C, 64.0; H, 7.99; N, 11.2. Found: C, 63.9; H, 7.89; N, 11.2.

N-Carbobenzoxy-S-benzyl-L-cysteinyl-L-prolyl-L-leucine Methylamide.—One gram of 5% palladium on charcoal was added to a solution of 3.0 g of N-carbobenzoxy-L-prolyl-L-leucine methylamide in 120 ml of methanol. Hydrogen was bubbled through this mixture for 3 hr at 50°. The catalyst was then removed by filtration, and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in 6 ml of dimethylformamide and 4.0 g of *p*-nitrophenyl *N*-carbobenzoxy-*S*-benzyl-L-cysteinate[10] was added to it. The solution was allowed to stand at room temperature for 3 days, then 50 ml of ethyl acetate was added and the mixture was successively extracted with five 25-ml portions of a 5% solution of $KHCO_3$, 25 ml of water, three 25-ml portions of 1 *N* HCl, and 25 ml of water. The organic solution was then dried ($MgSO_4$) and the solvent was removed by evaporation *in vacuo* to give an oily residue, which was dissolved in 5 ml of ethyl acetate. Hexane was added until this solution became cloudy. The product began to separate at room temperature in the form of needles. After the addition of 50 ml of a mixture of hexane and ethyl acetate (10:1) the crystalline suspension was kept overnight at 4°. The product was then collected by filtration, washed with hexane, and dried ($CaCl_2$ and KOH) to give 7.2 g, mp 74–76°. Recrystallization from ethyl acetate–hexane gave 3.2 g, mp 75–76°, $[\alpha]^{21}D$ −68.0° (*c* 1, ethanol).

Anal. Calcd for $C_{30}H_{40}N_4O_5S$: C, 63.4; H, 7.11; N, 9.85. Found: C, 63.3; H, 7.12; N, 9.84.

N-Tosyl-S-benzyl-L-cysteinyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparagine.—To a solution of 2.2 g of *N*-tosyl-*S*-benzyl-L-cysteinyl-L-tyrosine[25] in 30 ml of peroxide-free tetrahydrofuran was added 0.6 ml of triethylamine and the mixture was cooled to −10° and kept at that temperature for 5 min. Then 0.62 g of isobutyl chloroformate in 20 ml of tetrahydrofuran was added and the mixture was stirred at −10° for 20 min. A solution of 1.5 g of L-isoleucyl-L-glutaminyl-L-asparagine[26] in 11 ml of water and 0.6 ml of triethylamine was added to the reaction mixture, which was then stirred at room temperature for 1.5 hr. It was acidified by the slow addition of concentrated HCl, and the tetrahydrofuran was removed by evaporation *in vacuo*. After the addition of 20 ml of water to the residue, the insoluble material was collected by filtration and washed with 1 *N* HCl and H_2O. It was dissolved with mild heating in a mixture of 60 ml of tetrahydrofuran and 20 ml of H_2O. The solution was allowed to stand at room temperature for 2 days, in which time crystalline material gradually separated. It was collected by filtration and dried to give 2.5 g, mp 226–228° dec, $[\alpha]^{20}D$ +5.0° (*c* 1, dimethylformamide), lit.[12] mp 239–241° dec, $[\alpha]^{21}D$ +5.1° (*c* 1, dimethylformamide).

N-Tosyl-S-benzyl-L-cysteinyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-L-leucine Methylamide.—*N*-Carbobenzoxy-*S*-benzyl-L-cysteinyl-L-prolyl-L-leucine methylamide (2.8 g) was dissolved in 40 ml of glacial acetic acid and was treated with 40 ml of a 29% solution of HBr in acetic acid. The mixture was allowed to stand at room temperature for 20 min, then was poured into 300 ml of cooled, anhydrous ether. The ether was decanted and the solid hydrobromide of the tripeptide methylamide which had separated was washed twice by decantation of ether. It was then dissolved in 50 ml of methanol and the free base was liberated by stirring the solution with Rexyn RG 1 (OH form) until its pH was approximately 7. The resin was removed by filtration and washed with methanol. The combined filtrate and washings were evaporated *in vacuo*, and the residue was dissolved in 5 ml of dimethylformamide.

Dicyclohexylcarbodiimide (0.52 g) was added to a suspension of 0.88 g of *N*-tosyl-*S*-benzyl-L-cysteinyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparagine in 10 ml of dimethylformamide, and the mixture was stirred for 5 min at 5°. The solution of *S*-benzyl-L-cysteinyl-L-prolyl-L-leucine methylamide in dimethylformamide was added, and stirring was continued for 1 hr at 5°, for 3 hr at room temperature, and then for 30 min after the addition of 1 ml of glacial acetic acid. The dicyclohexylurea was removed by filtration and the filtrate was poured into 200 ml of water. The precipitated solid was collected by filtration washed successively with 1 *N* HCl, H_2O, a 5% solution of $KHCO_3$, and H_2O, dried *in vacuo* (P_2O_5), and dissolved in 20 ml of dimethylformamide. The peptide derivative was then precipitated by the addition of H_2O. After being kept at 4° overnight, the product was collected by filtration, washed with ice-cold H_2O, and dried (P_2O_5), to give 1.1 g, mp 255–257° dec, $[\alpha]^{21}D$ −31.0° (*c* 1, dimethylformamide).

Anal. Calcd for $C_{63}H_{85}N_{11}O_{13}S_3$: C, 58.2; H, 6.59; N, 11.8. Found: C, 58.0; H, 6.62; N, 11.8.

9-Decarboxamido-oxytocin.—A solution of 250 mg of the protected octapeptide methylamide in approximately 200 ml of boiling anhydrous ammonia, freshly distilled from sodium, was treated with sodium until the entire solution became blue and remained so for 5 min. The color was then discharged by the addition of 225 mg of NH_4Cl, and the ammonia was removed by lyophilization. The residue was dissolved in 350 ml of glass-distilled water. This solution was extracted with five 100-ml portions of ether to remove the thiocresol and the pH was adjusted to 7.0 by the addition of dilute acetic acid. To the stirred solution was added 100 ml of an 0.01 *M* solution of potassium ferricyanide, and stirring was continued for 20 min. Removal of the ferrocyanide and excess ferricyanide ions was accomplished

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

(16) P. Holton, *Brit. J. Pharmacol.*, **3**, 328 (1948).

(17) R. A. Munsick, *Endocrinology*, **66**, 451 (1960).

(18) B. A. Cross and G. W. Harris, *J. Endocrinol.*, **8**, 148 (1952).

(19) H. B. van Dyke, K. Adamsons, Jr., and S. L. Engel, *Recent Progr. Hormone Res.*, **11**, 1 (1955).

(20) W. Y. Chan, *J. Pharmacol. Exptl. Therap.*, **147**, 48 (1964).

(21) "The Pharmacopeia of the United States of America," 16th Rev., Mack Publishing Co., Easton, Pa., 1960, p 793.

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(23) W. H. Saywer, *Endocrinology*, **63**, 694 (1958).

(24) All melting points (corrected) were taken on a Thomas–Hoover melting point apparatus.

(25) (a) J. Honzl and J. Rudinger, *Collection Czech. Chem. Commun.*, **20**, 1190 (1955); (b) V. du Vigneaud, M. F. Bartlett, and A. Jöhl, *J. Am. Chem. Soc.*, **79**, 5572 (1957).

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

by passing the solution through a column of the weakly basic anion-exchange resin, Dowex AG 3-X4, in the chloride cycle. No avian depressor activity was detected in the deionized solution. The volume of the solution was reduced to approximately 40 ml by evaporation in a rotary evaporator, and the concentrated solution was put onto a column of Sephadex G-25 (100–200 mesh), which had been equilibrated with lower phase of the solvent system water(containing 3.5% acetic acid and 1.5% pyridine)–1-butanol–benzene (8:6:1),. The upper phase of this system was used for elution and one hundred 10-ml. fractions were collected. Folin–Lowry color values[27] of aliquots from every second fraction were plotted, and fractions corresponding to a peak having its maximum at fraction 55 (R_f ~0.2) were pooled, concentrated, and lyophilized, to give 41 mg, $[\alpha]^{21}D$ −24.0° (*c* 0.5, 1 *N* acetic acid).

Anal. Calcd for $C_{42}H_{65}N_{11}O_{11}S_2$: C, 52.3; H, 6.80; N, 16.0. Found: C, 52.3; H, 6.88; N, 15.7.

A sample of this material was hydrolyzed in 6 *N* HCl at 110° for 22 hr and was analyzed on a Beckman/Spinco amino acid analyzer,[28] operating the short column at 30° to effect separation of the methylamine and the ammonia. The molar ratios obtained, taking aspartic acid as 1, were: aspartic acid 1.0, glutamic acid 1.0, proline 1.0, cystine 0.95, isoleucine 1.0, leucine 1.0, tyrosine 0.9, ammonia 2.0, methylamine 1.0.

Acknowledgments.—The authors are indebted to the following members of this laboratory for their help in the course of the work: Dr. W. D. Cash for advice during the synthesis of *N*-carbobenzoxy-*S*-benzyl-L-cysteinyl-L-prolyl-L-leucine methylamide, Mr. Joseph Albert for the elemental microanalyses, Mr. Roger Sebbane for the amino acid analyses, and Mrs. Sherilyn Goodwin, Mrs. Marilyn Rippe, and Miss Margitta Wahrenburg, under the direction of Dr. W. Y. Chan, for the biological assays.

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

Mammalian Antifertility Agents. III. 1-Aryl-2-phenyl-1,2,3,4-tetrahydro-1-naphthols, 1-Aryl-2-phenyl-3,4-dihydronaphthalenes, and Their Derivatives[1]

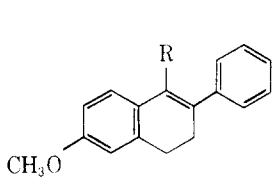
DANIEL LEDNICER, STANLEY C. LYSTER, BROOKE D. ASPERGREN, AND GORDON W. DUNCAN

Research Laboratories, The Upjohn Company, Kalamazoo, Michigan

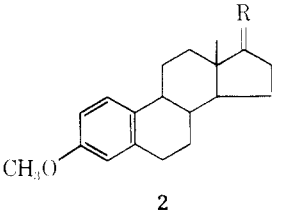
Received October 22, 1965

The preparation of a series of 1-aryl-2-phenyl-1,2,3,4-tetrahydro-1-naphthols and the corresponding 3,4-dihydronaphthalenes from 6-methoxy-2-phenyl-1-tetralone is described. The results of assays of these compounds as antifertility agents are reported. Biologic characterization showed that this activity in most cases be ascribed to the uterotropic activity of the compounds.

The preparation and structure–activity relationships of a series of diphenylindenes[2] and diphenylcoumarins[1] as antifertility agents have been previously reported. The sensitivity of the potency of given compounds of the previous series to structural modifications led us to investigate the naphthalene ring system (**1**) as a possibility for a further series of biologically active compounds. The resemblance of such a system to the A–B rings of the natural steroidal estrogens (**2**) lent further encouragement to these efforts.[3]



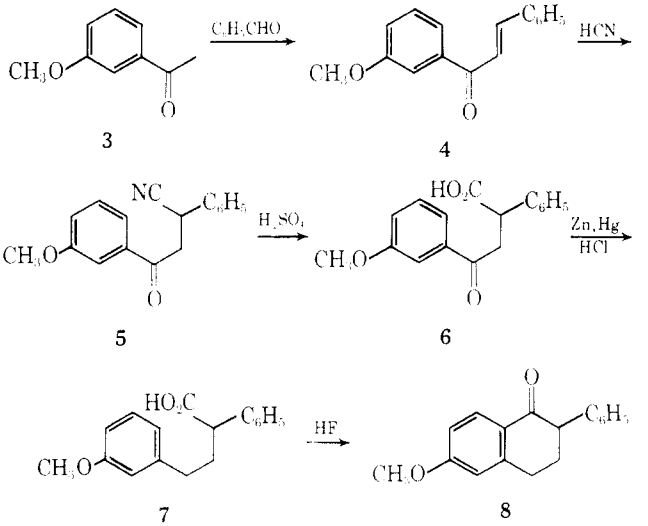
1



2

Preparation of 6-Methoxy-2-phenyl-1-tetralone.—The tetralone (**8**) upon which this series of compounds was based was originally prepared by a modification of Scheme I, first reported by Newman.[4,5]

SCHEME I



3 4 5 6 7 8

The cyanide addition and Clemmensen reduction proved difficult to carry out on large scale. The alternate route to **8** shown in Scheme II proved more convenient for scale up. Each of the steps went in a straightforward manner in workable yields.

1-Aryl-2-phenyl-1,2,3,4-tetrahydro-1-naphthols.—Reaction of the tetralone **8** with the appropriate aro-

(1) Previous paper in this series: D. Lednicer, S. C. Lyster, and G. W. Duncan, *J. Med. Chem.*, **8**, 725 (1965).

(2) D. Lednicer, J. C. Babcock, P. E. Marlatt, S. C. Lyster, and G. W. Duncan, *ibid.*, **8**, 52 (1965).

(3) Subsequent to the completion of this work a paper describing the preparation and biological activities of 6-deoxy-1,2-diphenyl-3,4-dihydronaphthalenes has appeared: W. L. Benezc, L. I. Barsky, W. P. Sopchak, A. A. Renzi, N. Howie, and J. J. Chart, *ibid.*, **8**, 213 (1965).

(4) M. S. Newman, *J. Am. Chem. Soc.*, **60**, 2947 (1938).

(5) D. Lednicer, J. C. Babcock, S. C. Lyster, and G. W. Duncan, *Chem. Ind.* (London), 408 (1963).