solid which formed was poured into an ice-cold water solution containing NH_4Cl. Two layers separated. The aqueous layer was extracted thoroughly with ether and the ether extract was dried (Na_2SO_4). The drying salt was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. A yellow oil was obtained which crystallized on standing in the refrigerator. This substance was recrystallized from ethyl alcohol to afford 5.8 g of peach-colored crystals, mp 45–47°.

1,1-Dimethyl-3-dimethylaminomethyl-2-tetralone Hydrochloride (12).—A mixture of 19.6 g. (0.113 mole) of 1,1-dimethyl-2-tetralone, 9.2 g (0 128 mole) of dimethylamine hydrochloride, and 3.8 g (0.043 mole) of paraformaldehyde dissolved in 75 ml of ethyl alcohol containing 0.2 ml of concentrated HCl was heated at reflux for 8 hr. The solution was filtered from a small amount of solid material and the filtrate was evaporated to dryness *in vacuo*. The resulting white powder was recrystallized three times from ethyl alcohol to yield 7.0 g of Mannich base hydrochloride, mp 149–150°.

Compound 14 was prepared by a similar procedure.

The Mannich base 12 (6.9 g.) was dissolved in CH_3OH and 4.6 g of $NaBH_4$was added portionwise. The solution was then heated on the steam bath for 3 hr and then evaporated to a yellow paste. The semisolid material was treated with 500 ml of an aqueous saturated NaCl solution which was in turn extracted several times with ether. The yellow ether extract was dried (Na_2SO_4). The salt was removed by filtration and the filtrate was evaporated to a light yellow oil. An infrared spectrum revealed that very little ketone was present. The acetate derivative of the carbinol, **1,1-dimethyl-3-dimethylaminomethyl-2-tetralol,** was prepared in the usual way to give 1.0 g of **13,** mp 233–234°.

2-Amino-4,9-dihydro-4,4-dimethylnaphtho[2,3-*d*]thiazole Hydrobromide.—An ether solution of 1,1-dimethyl-2-tetralone (10.0 g, 0.058 mole) was treated dropwise with stirring with 9.2 g (0.057 mole) of Br_2. The resulting pale yellow solution was evaporated to dryness *in vacuo*, the temperature being maintained below 15°, to give an orange oil which resisted all attempts to crystallize. This oil (14.5 g, 0.0586 mole) was dissolved in 100 ml of ethyl alcohol to which solution then was added 4.4 g (0.058 mole) of thiourea. The solution was heated under reflux for 3 hr. One-half of the solvent was removed *in vacuo* and the resulting solution was treated with excess ether. An oil separated from the solution This oil was triturated with acetone to give a white powder which was recrystallized from excess acetone to yield 5.2 g of product, mp 240–242°.

Anal. Calcd for $C_{13}H_{15}BrN_2S$: C, 50.20; H, 4.86; N, 9.01. Found: C, 50.24; H, 4.79; N, 8.74.

3-Bromo-1,1-dimethyl-5-methoxy-2-tetralone, mp 110–112°, was prepared as described above. It was treated directly with thiourea in ethyl alcohol to form 2-amino-4,9-dihydro-4,4-dimethyl-8-methoxynaphtho[2,3-*d*]thiazole hydrobromide, mp 276–277°.

Anal. Calcd for $C_{14}H_{17}BrN_2OS$: C, 49.31; H, 5.03; N, 8.22. Found: C, 49.57; H, 5.12; N, 7.95.

Ring-D-Bridge Steroid Analogs. IV.[1] 14α,17α-Ethenopregn-4-ene-3,20-dione[2]

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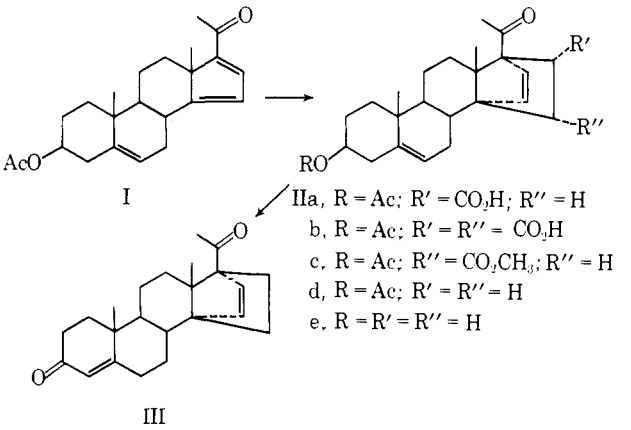
Recently[1,4,5] we have been attempting to synthesize 14α,17α-bridged analogs of steroid hormones, in order to determine the effect of such bridging on the biological activity of the hormones. Diels–Alder additions to the diene system of $\Delta^{14,16}$-steroids have afforded adducts[4,5] which are potentially suitable for transformation into progesterone analogs. The ring-D double bonds of the adducts,[5] formed by reaction of such steroidal dienes with maleic anhydride or with 4-phenyl-1,2,4-triazoline-3,5-dione, could not be reduced selectively by low-pressure catalytic hydrogenation.[6] However, such double bonds were sufficiently susceptible to intramolecular attack to prevent the oxidative decarboxylation of *endo*-carboxylic acids. Thus, an attempted Hunsdiecker reaction on IIa resulted in the formation of a halolactone,[1] and an attempted bisdecarboxylation[7] of the diacid IIb gave a complex mixture which had an infrared spectrum consistent with the presence of some of the expected[8] dilactone.

Conditions have recently been found[9] which permit the selective catalytic hydrogenation of the ring-D double bond of the acrylate adduct IIc,[4] and an attempt to degrade this reduced adduct to a simple 14α,17α-etheno- (or ethano-) bridge analog is currently being made. While the above work was in progress, a more direct approach to the desired hormone analogs was suggested by a report[10] that pressures greater than 1000 atm facilitate the addition of ethylene to dimethyl cyclohexa-1,3-diene-1,4-dicarboxylate.

Heating a benzene solution of 3β-acetoxy-20-keto-5,14,16-pregnatriene[11] (I) at 160° for 14 hr under 3000 atm of ethylene led to the formation of 14α,17α-ethenopregn-5-en-3β-ol-20-one acetate (IId) in 53% yield. The close similarity, particularly in the vinyl hydrogen region, of the nmr spectrum of IId to those of closely related Diels–Alder adducts[4,5] supports its gross structure; this evidence together with the stereospecificity of the above reaction led us to assign the stereochemistry of IIa on the basis of the same analogy.[4,5] Hydrolysis of the acetate group of IId fol-



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lowed by oxidation[12] afforded 14α,17α-ethenopregn-4-ene-3,20-dione (III).

Progesterone analog III was assayed for activity by the modified Clauberg Assay.[13] Preliminary results indicate that a total dose of 0.2 mg of III, administered by subcutaneous injections, elicits an average response of 1.5+; an equal dose of progesterone elicited a response of 0.5+. Since III may be regarded as a frozen rotomer of a 17α-alkylprogesterone, it seems of interest to note that its activity appears to be at least as great as that reported for 17α-ethylprogesterone.[14]

Experimental Section[15]

14α,17α-Ethenopregn-5-en-3β-ol-20-one Acetate (IId).—A solution of 6.0 g of I in 75 ml of benzene was heated at 160° under ethylene at 3000 atm for 14 hr. Then the mixture was cooled, filtered, and evaporated to dryness under reduced pressure. The residue was taken up in methanol and filtered to remove the insoluble polyethylene. The residue, obtained by distilling the filtrate, was chromatographed over 125 g of acid-washed alumina (hexane–benzene). Crystallization from methanol gave IId, in a yield of 3.44 g (53%) as white rods: mp 140–142°; ν^{Nujol} 1730, 1701 cm^{-1}. The vinyl protons appeared in the nmr spectrum at δ 5.45 (m), 6.05 (d, J = 6 cps), and 6.16 (d, J = 6 cps).

Anal. Calcd for $C_{25}H_{34}O_3$: C, 78.49; H, 8.96. Found: C, 78.31; H, 9.12.

14α,17α-Ethenopregn-5-en-3β-ol-20-one (IIe).—After a mixture of 1.44 g of IIa, 1.46 g of KOH, 6 ml of water, and 50 ml of ethanol had been stirred at room temperature for 20 hr, it was concentrated under vacuum and then partitioned between ether and water. The ether extract was dried ($MgSO_4$) and then evaporated to dryness under reduced pressure. Crystallization from ethanol afforded IIe, in a yield of 1.12 g (87%), as white needles: mp 196–198°; ν^{Nujol} 3636, 1675 cm^{-1}. The nmr spectrum showed a singlet at δ 2.18 (21-CH_3) and peaks at 5.42, 6.05, and 6.17 corresponding to the 6, 15, and 16 protons, respectively.

Anal. Calcd for $C_{23}H_{32}O_2$: C, 81.13; H, 9.47. Found: C, 80.91; H, 9.36.

14α,17α-Ethenopregn-4-ene-3,20-dione (III).—A mixture of 1.52 g of IIe, 9.5 ml of cyclohexanone, and 180 ml of toluene was azeotroped under a Dean–Stark head for 1.5 hr. Then, 1.68 g of aluminum isopropoxide was added and reflux continued for 1.5 hr. After the resulting solution had been cooled to room temperature, it was washed with aqueous HCl, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed over 45 g of Woelm neutral alumina, activity grade I. After impurities had been eluted by benzene–hexane mixtures, fractions containing the product were eluted by 100 ml of benzene followed by 100 ml of 10% ethyl acetate in benzene. These fractions were crystallized from acetone–hexane to afford III in a yield of 990 mg (59%) as light yellow crystals: mp 151–152°; ν^{Nujol} 1678, 1625 cm^{-1}. The nmr spectrum showed a singlet at δ 2.17 (21-CH_3), a multiplet at 5.76 (C_4 vinyl hydrogen), and a singlet at 6.07 (C_{15} and C_{16} vinyl hydrogens).

Anal. Calcd for $C_{23}H_{30}O_2$: C, 81.61; H, 8.93. Found: C, 81.64; H, 9.02.

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Synthetic Bradykinin Analogs

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In continuing our study[1] of substituent effects on the biological activity of bradykinin a further series of six analogs has been prepared and tested in the guinea pig lung and on blood pressure.[2] The analogs were synthesized by the stepwise elongation of the peptide chain as described in earlier publications[3] utilizing for the most part the *p*-nitrophenyl ester method. The intermediate peptides and the final products are listed in Table I. All of the peptides from the carbobenzoxyhexapeptide to the tricarbobenzoxynonapeptide were found to contain an O-acetyl group on the serine hydroxyl as previously reported.[4]

The method of Filler and Novar[5] was used for the preparation of *m*-trifluoromethylphenylalanine. The N-acetyl derivative was resolved into its optical isomers with L-*threo*-*p*-nitrophenyl-2-amino-1,3-propanediol.

The biological activities of the six analogs are given in Table II. The results obtained for the 4-sarcosine and the glycyl bradykinin are in the range of those reported by Schröder and Hempel[6] for these compounds; however, no details of preparation were given. The results of the 5-D-phenylalanine analog should be viewed with some skepticism since even a small amount of the L isomer would lead to an erroneous interpretation of the data obtained.[1] Of considerable interest is the activity found for the 8-*m*-trifluoromethylphenylalanine analog. This peptide is about 1.5 times as active as bradykinin in lowering guinea pig blood pressure, but only one-half as active in the lung bronchoconstriction. This finding lends support to the receptor-site theory advanced by Scherrer[7] and also would support a view that different receptor sites are involved in the bronchoconstrictive and hypotensive effects observed.

Experimental Section

***m*-Trifluoromethyl-L- and -D-phenylalanine.**—To a solution of 42 g (0.155 mole) of *m*-trifluoromethyl-DL-phenylalanine[8] in 75 ml of methanol was added 33 g (0.155 mole) of L-*threo*-*p*-nitrophenyl-2-amino-1,3-propanediol. The mixture was warmed to effect solution and 300 ml of ethyl acetate was added. A white solid crystallized was removed and dried; 36 g, mp 185–186°, $[\alpha]^{28}D$ −46° (*c* 2, methanol). The mother liquor was evaporated to a small volume and ethyl acetate was added giving 37 g of white solid which was recrystallized from ethyl acetate containing a small amount of methanol; 34 g, mp 184–185°, $[\alpha]^{28}D$ −46° (*c* 2, methanol). The two salts were converted to the free acids by treatment with dilute HCl and extraction with

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