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.

Acknowledgments.—We are deeply grateful to Dr. J. C. Kauer and to the E. I. du Pont de Nemours and Co. for carrying out the high pressure addition of ethylene to I.

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(15) Melting points were determined in capillary tubes on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn. The infrared spectra were determined on a Perkin-Elmer Infracord Model 137. Nmr spectra were determined in $CDCl_3$ on a Varian A-60 spectrometer and are reported in parts per million downfield from a tetramethylsilane internal standard.

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°, $[\alpha]^{25}D$ +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°, $[\alpha]^{25}D$ −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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(2) The authors are indebted to Dr. H. O. J. Collier and associates for the biological testing of the analogs in the guinea pig.

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TABLE I

Compound	Formula	$[\alpha]_D$, deg (c 1, DMF)	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
Cbz-Sar-Phe-Ser-Pro-Phe-NO_2-Arg-OCH_3	$C_{46}H_{58}N_{10}O_{13}$	−45	184–189	57.61	6.10	14.63	57.35	5.96	14.86
Cbz-Pro-Sar-Phe-Ser-Pro-Phe-NO_2-Arg-OCH_3	$C_{51}H_{65}N_{11}O_{14}$	−48.5	120–125	58.00	6.20	14.65	57.24	6.06	14.50
Cbz-Pro-Pro-Sar-Phe-Ser-Pro-Phe-NO_2-Arg-OCH_3	$C_{56}H_{72}N_{12}O_{15}$	−70	140–145	58.20	6.29	14.57	58.06	6.13	14.97
TriCbz-Arg-Pro-Pro-Sar-Phe-Ser-Pro-Phe-NO_2-Arg-OCH_3	$C_{78}H_{96}N_{16}O_{20}$	−66	120–125	59.40	6.13	14.20	58.81	6.28	14.44
DiCbz-Arg-Pro-Pro-Sar-Phe-Ser-Pro-Phe-NO_2-Arg	$C_{67}H_{86}N_{16}O_{17}\cdot H_2O$	−62.5	160–165	57.15	6.28	15.93	57.16	6.26	16.07
Arg-Pro-Pro-Sar-Phe-Ser-Pro-Phe-Arg-triacetate	$C_{57}H_{87}N_{15}O_{17}\cdot 4H_2O$	−81.2 (c 1, H_2O)		51.60	7.23	15.87	51.71	7.20	16.29
Cbz-5-NH_2Val-Phe-Ser-Pro-Phe-NO_2-Arg-OCH_3	$C_{48}H_{62}N_{10}O_{13}$	−51	190–193	58.41	6.33	14.21	58.18	6.13	14.67
Cbz-Pro-5-NH_2Val-Phe-Pro-Ser-Phe-NO_2-Arg-OCH_3	$C_{53}H_{69}N_{11}O_{14}$	−60	211–215	58.65	6.43	14.22	58.65	6.49	14.43
Cbz-Pro-Pro-5-NH_2Val-Phe-Ser-Pro-Phe-NO_2-Arg-OCH_3	$C_{58}H_{76}N_{12}O_{15}$	−65	185–190	58.98	6.47	14.22	58.98	6.45	14.38
TriCbz-Arg-Pro-Pro-5-NH_2Val-Phe-Ser-Pro-Phe-NO_2-Arg-OCH_3	$C_{80}H_{100}N_{16}O_{20}$	−55.6	155–157	59.75	6.26	13.97	59.16	6.20	14.09
DiCbz-Arg-Pro-Pro-5-NH_2Val-Phe-Ser-Pro-Phe-NO_2-Arg	$C_{69}H_{90}N_{16}O_{17}\cdot H_2O$	−51.4	153–160	57.84	6.40	15.65	57.65	6.36	15.73
Arg-Pro-Pro-5-NH_2Val-Phe-Ser-Pro-Phe-Arg-triacetate	$C_{59}H_{91}N_{15}O_{17}\cdot 2H_2O$	−78.8 (c 1, H_2O)	140–146	55.15	7.14	16.40	54.96	7.00	16.91
Cbz-D-Phe-Ser-Pro-Phe-NO_2-Arg-OCH_3	$C_{41}H_{51}N_9O_{11}\cdot 0.5H_2O$[a]	−31	150–153	57.60	6.25	14.74	57.67	6.19	14.73
Cbz-Gly-D-Phe-Ser-Pro-Phe-NO_2-Arg-OCH_3	$C_{43}H_{56}N_{10}O_{13}$	−34	85–120	57.20	5.97	14.83	57.37	6.05	14.46
Cbz-Pro-Gly-D-Phe-Ser-Pro-Phe-NO_2-Arg-OCH_3	$C_{50}H_{63}N_{11}O_{14}$	−54	105–130	57.62	6.09	14.78	57.83	5.99	14.67
Cbz-Pro-Pro-Gly-D-Phe-Ser-Pro-Phe-NO_2-Arg-OCH_3	$C_{55}H_{70}N_{12}O_{15}$	−49.5	125–140	57.99	6.19	14.76	58.63	6.29	14.54
TriCbz-Arg-Pro-Pro-Gly-D-Phe-Ser-Pro-Phe-NO_2-Arg-OCH_3	$C_{77}H_{94}N_{16}O_{20}$	−53	120–125	59.14	6.06	14.34	59.23	6.27	14.76
DiCbz-Arg-Pro-Pro-Gly-D-Phe-Ser-Pro-Phe-NO_2-Arg	$C_{66}H_{84}N_{16}O_{17}\cdot H_2O$	−54	180–200	56.96	6.23	16.16	57.05	6.29	16.27
Arg-Pro-Pro-Gly-D-Phe-Ser-Pro-Phe-Arg-triacetate	$C_{56}H_{85}N_{15}O_{17}$	−78.8 (c 1, H_2O)	173–183	54.00	6.90	16.90	53.76	7.07	17.37
Cbz-Pro-Gly-Gly-Phe-Ser-Pro-Phe-NO_2-Arg-OCH_3	$C_{52}H_{66}N_{12}O_{15}$	−58.5	233–234	56.82	6.05	15.29	56.88	6.04	15.11
Cbz-NO_2-Arg-Pro-Pro-Gly-Gly-Phe-Ser-Pro-NO_2-Arg-OCH_3	$C_{63}H_{85}N_{18}O_{19}\cdot 2H_2O$	−52	200–210	52.75	6.25	17.62	52.75	6.25	17.70
Cbz-NO_2-Arg-Pro-Pro-Gly-Gly-Phe-Ser-Pro-Phe-NO_2-Arg	$C_{60}H_{79}N_{18}O_{18}\cdot H_2O$[b]	−43.5	170–175	53.05	6.01	18.56	52.97	5.99	18.05
Arg-Pro-Pro-Gly-Gly-Phe-Ser-Pro-Phe-Arg-triacetate	$C_{58}H_{88}N_{16}O_{18}$	−66 (c 1, H_2O)		53.69	6.83	17.28	52.37	6.87	17.23
Cbz-Gly-NO_2-Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-NO_2-Arg-OCH_3	$C_{63}H_{84}N_{18}O_{19}$	−61	140–150	54.15	6.06	18.04	53.85	6.16	17.63
Cbz-Gly-NO_2-Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-NO_2-Arg	$C_{61}H_{80}N_{18}O_{18}$	−51.1	180–185	53.72	6.01	18.80	53.60	6.21	18.83
Gly-Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg-triacetate	$C_{58}H_{88}N_{16}O_{18}\cdot 3H_2O$	−85.6 (c 1, H_2O)		51.54	7.01	16.58	51.75	6.88	16.67
Cbz-*m*-CF_3Phe-NO_2-Arg-OCH_3	$C_{25}H_{29}F_3N_6O_7$	−10	75–80	51.54	5.02	14.43	51.62	5.22	14.64
Cbz-Pro-*m*-CF_3Phe-NO_2-Arg-OCH_3	$C_{30}H_{36}F_3N_7O_8$	−38	85–100	53.02	5.34	14.43	53.29	5.58	14.46
Cbz-Phe-Ser-Pro-*m*-CF_3Phe-NO_2-Arg-OCH_3	$C_{42}H_{50}F_3N_9O_{11}$	−35	160–162	55.20	5.52	13.80	55.54	5.69	13.82
Cbz-Gly-Phe-Ser-Pro-*m*-CF_3Phe-NO_2-Arg-OCH_3	$C_{46}H_{53}F_3N_{10}O_{12}$	−51	208–210	54.53	5.47	13.83	54.46	5.57	13.97
Cbz-Pro-Gly-Phe-Ser-Pro-*m*-CF_3Phe-NO_2-Arg-OCH_3	$C_{51}H_{62}F_3N_{11}O_{14}$	−60	195–197	55.18	5.63	13.88	55.02	5.61	14.04
Cbz-Pro-Pro-Gly-Phe-Ser-Pro-*m*-CF_3Phe-NO_2-Arg-OCH_3	$C_{56}H_{69}F_3N_{12}O_{15}$	−60	148–152	55.71	5.76	13.92	54.90	5.75	13.95
TriCbz-Arg-Pro-Pro-Gly-Phe-Ser-Pro-*m*-CF_3Phe-NO_2-Arg-OCH_3	$C_{78}H_{93}F_3N_{16}O_{20}$	−54	130–140	57.41	5.74	13.74	56.93	5.81	13.53
DiCbz-Arg-Pro-Pro-Gly-Phe-Ser-Pro-*m*-CF_3Phe-NO_2-Arg	$C_{67}H_{83}F_3N_{16}O_{17}\cdot 3H_2O$[c]	−50	175–180	53.81	6.00	14.99	54.21	6.02	15.02
Arg-Pro-Pro-Gly-Phe-Ser-Pro-*m*-CF_3Phe-Arg-triacetate	$C_{57}H_{84}F_3N_{15}O_{17}\cdot 3H_2O$[d]	−79 (c 1, H_2O)		50.25	6.66	15.42	50.61	6.79	15.66

[a] *Anal.* Calcd: H_2O, 1.37. Found: H_2O, 1.42. [b] *Anal.* Calcd: H_2O, 1.33. Found: H_2O, 1.30. [c] *Anal.* Calcd: F, 3.81. Found: F, 3.75. [d] *Anal.* Calcd: F, 4.18. Found: F, 3.99

TABLE II

BIOLOGICAL ACTIVITY OF BRADYKININ ANALOGS

Analog	μg equivalent to 1 μg of bradykinin in guinea pig: Lung	Blood pressure
4-Sar bradykinin	1000	33
5-(5-NH_2Val) bradykinin	1000	60
5-D-Phe bradykinin	33	40
4-Homogly bradykinin	>10	70
Glycyl bradykinin	4	2–4
8-*m*-CF_3Phe bradykinin	2	0.67

ethyl acetate. The ethyl acetate solutions were evaporated, and the residues were suspended in 300 ml of 2 *N* HCl and refluxed for 12 hr. The solutions were evaporated to one-third volume and the pH was brought to 7 with concentrated NH_4OH. The precipitates were removed, washed with cold water, and dried. The L isomer melted at 210–211°, $[\alpha]^{24}D$ −14° (*c* 1, water) and the D isomer at 210–212°, $[\alpha]^{24}D$ +14° (*c* 1, water).

Carbobenzoxy-*m*-trifluoromethyl-L-phenylalanine.—The reaction of 8.5 g (0.0355 mole) of *m*-trifluoromethyl-L-phenylalanine with carbobenzoxy chloride gave 12.5 g (96%) of a white solid, mp 106–107°, $[\alpha]^{25}D$ −2° (*c* 1, methanol).

Anal. Calcd for $C_{18}H_{16}F_3NO_4$: C, 58.86; H, 4.40; N, 3.82. Found: C, 58.59; H, 4.41; N, 3.69.

Carbobenzoxy-*m*-trifluoromethyl-L-phenylalanine *p*-nitrophenyl ester was obtained as a cream-colored solid in 87% yield using *p*-nitrophenol and dicyclohexylcarbodiimide, mp 106–107°, $[\alpha]^{25}D$ −30° (*c* 1, methanol).

Anal. Calcd for $C_{24}H_{19}F_3N_2O_6$: C, 59.02; H, 3.92; N, 5.73. Found: C, 59.23; H, 3.98; N, 5.80.

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2,8-Bis(substituted amino)phenothiazine 5,5-Dioxides[1]

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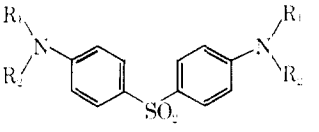
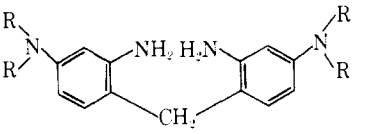
The synthesis of bis(4-aminophenyl) sulfone (Ia, 4,4'-diaminodiphenyl sulfone, DDS) and its acetylated derivative, Ib (DADDS), was reported in 1908.[2] Compounds of this type were found to possess antistreptococcal activity (approximately 30 times that of sulfanilamide) and have been used in the treatment of some common bacterial infectious diseases.[3] Later, DDS and its derivatives were recognized as being useful in the treatment of tuberculosis[4] and leprosy.[5] During the Second World War, the antimalarial activity of a number of compounds in this series was unveiled in screening processes.[6] In 1960, Archibald and Ross[7] reported the use of DDS in the treatment of falciparum and quartan malaria in natives living in hyperendemic areas. The importance of DDS and related compounds has recently been demonstrated by the fact that many chloroquine-resistant strains of malaria parasites did not show cross-resistance to DDS.[8,9] Structure–activity relationship studies revealed that, in general, the antimalarial activity of compounds of this type is lost when tertiary amino groups or non-hydrogen-bonding substituents are present at the *para* (4 and 4') positions or when the *p*-amino functions are changed to the *meta* (3 and 3') positions. On the other hand, changing to small secondary amino or acylamido groups at the *para* positions[10] and/or certain substitution at the *ortho* (2 and 2') positions[6] does not alter and may even enhance antimalarial activity.

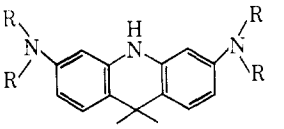


Ia, R_1, R_2 = H
b, R_1 = H; R_2 = CH_3CO

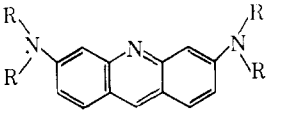
Two 2,4-bis(substituted amino)diphenylmethanes (IIa and IIb) were shown to possess antimalarial activity in avian malaria. Billman, *et al.*,[15] proposed that these compounds could actually be considered as precursors of the acridine derivative (IV), since it has been reported that compounds of type II could conceivably be deaminated to give the intermediate dihydroacridines (III), which are readily oxidized by oxygen or ferric chloride to form IV.[16]



IIa, R = CH_3
b, R = C_2H_5



III



IV

A number of phenothiazines are known to display a variety of physiological activities. Methylene blue, a tetramethyl derivative of Lauth's violet (3,6-diaminophenothiazonium chloride), was found to have some

(1) This investigation was supported by the Walter Reed Army Institute of Research (WRAIR), Walter Reed Army Medical Center, Department of the Army, and Headquarters, U.S. Army Medical Research and Development Command, Office of the Surgeon General, Contract No. DA-49-193-MD-2749. This paper is Contribution No. 132 from the Army Research Program on Malaria.

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