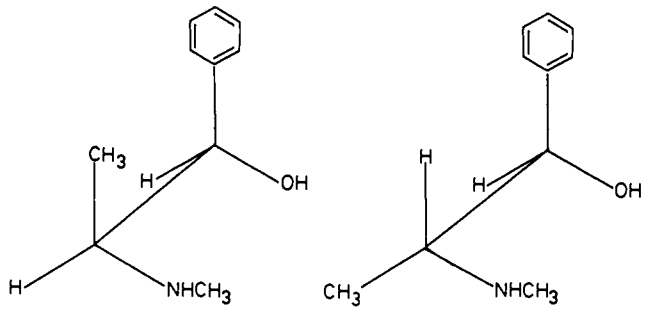
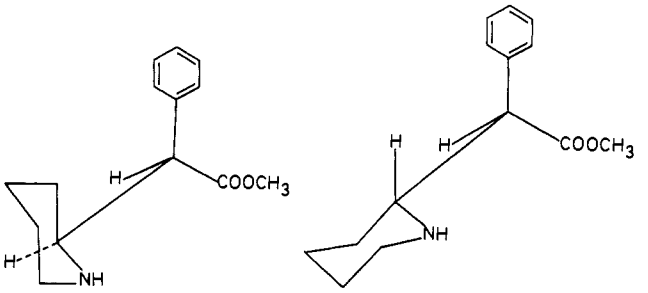


D(−)Ephedrine D(−)Pseudoephedrine

Fig. 1.—Relationship of the functional groups in the D-diastereoisomers, ephedrine and pseudoephedrine (preferred conformations not implied).



erythro-Methylphenidate *threo*-Methylphenidate

Fig. 2.—Relationship of the functional groups in the D-diastereoisomers of methylphenidate (preferred conformations not implied).

At this dose level D(−)pseudoephedrine produced no pressor response whatever, and in fact, produced a small, transient drop in blood pressure. D(−)Ephedrine produced a rise in blood pressure of approximately 70 mm. If the test animal was pretreated with D(−)pseudoephedrine and given D(−)ephedrine one-half hour later, there was no pressor response, indicating that, at these doses, D(−)pseudoephedrine is capable of completely blocking the pressor effect of D(−)ephedrine.

Since D(−)pseudoephedrine itself did not produce any pressor response it was assumed that this was a true blockade and that cross-tachyphylaxis was not involved. This was borne out by the finding that D(−)pseudoephedrine given at the peak of the pressor response to D(−)ephedrine caused an immediate return of the blood pressure to normal. These effects were not obtained when the other ephedrine isomers (L(+)ephedrine, L(+)pseudoephedrine) were tested under the same conditions.

In a further series of experiments, it was found that pretreatment with D(−)pseudoephedrine blocked the pressor effect of tyramine and amphetamine, and augmented the pressor response of norepinephrine. In these respects the action of D(−)pseudoephedrine appears very similar to that reported for methylphenidate.[3,4] Methylphenidate (methyl-α-phenyl-2-piperidine acetate) contains two asymmetric carbon atoms, and therefore can exist in two diastereoisomeric forms, *erythro* and *threo*. When methylphenidate is represented as in Fig. 2, the resemblance to the isomers of ephedrine becomes apparent. This resemblance led us to make the assumption that the active racemate of methylphenidate is the *threo* racemate, and this has been stated by Druey,[5] recently. Although the absolute configurations of the isomeric methylphenidates are not known, we have drawn the *threo* enantiomorph which is configurationally identical to D(−)pseudoephedrine because the action of methylphenidate is essentially the same as the action of D(−)pseudoephedrine.

Burn and Rand[6] have demonstrated that ephedrine, tyramine, amphetamine, and certain other sympathomimetic amines act by releasing norepinephrine from storage sites. Muskus, *et al.*,[7] have suggested recently that ephedrine and norephedrine are compounds which have indirect activity (release of norepinephrine from storage sites) as well as direct activity (at effector site). The experiments described in this note indicate that D(−)pseudoephedrine blocks the pressor effects of ephedrine regardless of whether these effects are indirectly or directly produced. Investigations are being carried out to determine the exact nature of this blocking action.

Experimental

Preparation of the Isomers of Ephedrine.—Ephedrine alkaloid (Merck) was converted into a mixture of four isomers by boiling in *p*-cymene in the presence of sodium methoxide.[8,9] The two racemates were obtained by fractional crystallization. (±)-Ephedrine was resolved through formation of the (+)-mandelate salts according to Manske and Johnson.[10] (±)-Pseudoephedrine was resolved through formation of the (+)-tartrate salts according to Späth and Göhring.[11] These resolutions were carried out primarily to obtain L(+)ephedrine, and D(−)pseudoephedrine, neither of which is commercially available. D(−)Ephedrine was obtained from Merck and Company, and L(+)pseudo ephedrine from L. Light and Company, Ltd., England.

Acknowledgment.—This research was supported in part by a grant from the Development Fund of the Ohio State University.

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A Hydroxamic Acid Analog of Cortisone

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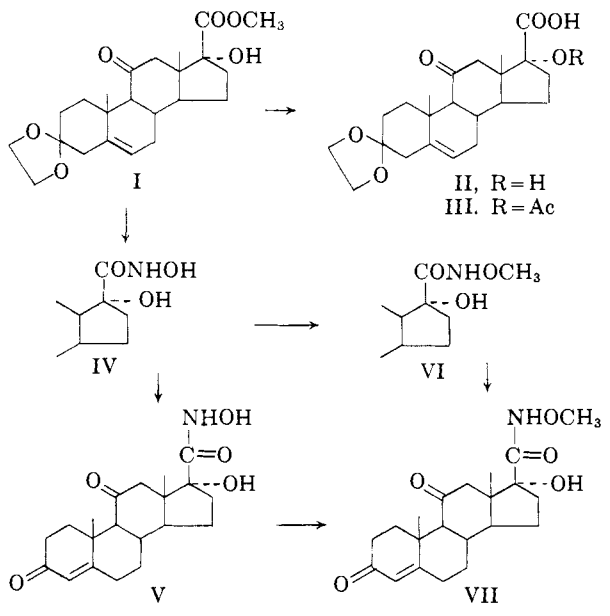
Numerous modifications have been carried out on the 21-hydroxymethylene grouping in the corticoid series[1]

(1) For leading references, see R. E. Schaub and M. J. Weiss, *J. Org. Chem.*, **26**, 1223 (1961); also H. D. Brown, A. R. Matzuk, D. R. Hoff and L. H. Sarett, *J. Org. Chem.*, **27**, 961 (1962); M. Marx and L. L. Smith, U. S. Patent 3,020,275 (Feb. 6, 1962); W. S. Allen and M. J. Weiss, *J. Org. Chem.*, **26**, 4153 (1961); H. D. Brown, A. R. Matzuk, D. R. Hoff and L. H. Sarett, *J. Org. Chem.*, **26**, 5052 (1961); J. Tóth, Z. Tuba and L. Szporny, *Nature*, **191**, 607 (1961); E. J. Agnello and G. D. Laubach, U. S. Patent 2,920,999 (Jan. 12, 1960); E. J. Agnello, R. Pinson, S. K. Figdor, G. M. K. Hughes, H. W. Ordway, B. M. Bloom and G. D. Laubach *Experientia*, **16**, 357 (1960).

and this approach has led to a number of biologically interesting steroids. It occurred to us that it might be of interest to prepare the corresponding hydroxamic acids in which the 21-hydroxymethylene is replaced by a hydroxylamino grouping. Recent reports[2] on the synthesis of certain steroidal cyclic hydroxamic acid derivatives (N-hydroxylactams) prompts us to communicate the results of our investigation.

Reaction of 17α-hydroxy-3,11-dioxo-4-etiocholenic acid methyl ester[3] with 2-methyl-2-ethyl-1,3-dioxolane[4] gave the ketal I. The latter compound readily was hydrolyzed with alcoholic potassium hydroxide, and acidification with a solution of dihydrogen sodium phosphate gave the acid II. Treatment of II with acetic anhydride in pyridine gave the corresponding acetate III. Both III and its corresponding sodium salt reacted with oxalyl chloride in the usual manner, with subsequent treatment with hydroxylamine under a variety of conditions. In every case intractable mixtures were obtained.



However, treatment of I with hydroxylamine in the presence of sodium methoxide gave the corresponding hydroxamic acid IV in 67.5% yield. Acid hydrolysis of the latter compound gave 17α-hydroxy-3,11-dioxo-4-etiocholenohydroxamic acid (V) in 72% yield (intense coloration with ferric chloride).

In order to prepare the corresponding O-methyl ether, the ketal IV was treated with sodium ethoxide and methyl iodide to give VI in 51% yield. Acid hydrolysis of VI gave O-methyl-17α-hydroxy-3,11-dioxo-4-etiocholenohydroxamic acid (VII) in 52% yield (negative ferric chloride reaction). In a more convenient procedure, compound V was alkylated directly with sodium ethoxide and methyl iodide to give VII in 81% yield.

Biological Activity.[5]—In intact rats, compounds V and VII showed no activity when assayed at 20 times the dose (by weight) of hydrocortisone, which gives a 50% thymus involution in this test. Both V and VII were inactive in the cotton pellet granuloma procedure. In adrenalectomized rats, both V and VII were inactive in the thymus involution assay and showed no anticorticoid activity when administered concurrently with hydrocortisone.

Experimental[6]

3-Cyclic Ethylene Acetal of 17α-Hydroxy-3,11-dioxo-4-etiocholenic Acid Methyl Ester (I).—A mixture of 19.28 g. of 17α-hydroxy-3,11-dioxo-4-etiocholenic acid methyl ester[3] in 320 ml. of 2-methyl-2-ethyl-1,3-dioxolane[4] and 600 mg. of *p*-toluenesulfonic acid was heated to boiling and was distilled slowly for 2.5 hr., about 200 ml. of distillate being collected in this time. The cooled reaction mixture was diluted with ether–methylene chloride (2.5:1) and was washed successively with 5% aqueous sodium bicarbonate and water. The organic layer was dried (Na_2SO_4) and concentrated to dryness under reduced pressure. Three crystallizations of the residue from methylene chloride–ether gave 10.48 g. of the crude ketal (I), m.p. 186–190.5°. Infrared examination of the residue from the mother liquors indicated the presence of a substantial amount of unreacted ketone. Consequently, the above procedure was repeated twice on the residues, to give a total of 16.39 g. (75.5% over-all yield) of crude I. Crystallization from methylene chloride–ether gave an analytical sample, m.p. 195.5–198°, $[\alpha]^{25}D$ −1.4° (*c*, 1.04), $\lambda_{max}^{CHCl_3}$ 2.83, 5.73 and 5.87 μ.

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.48; H, 8.11.

3-Cyclic Ethylene Acetal of 17α-Hydroxy-3,11-dioxo-4-etiocholenic Acid (II).—A solution of 14.53 g. of the crude ketal I (m.p. 186–190°) in 185 ml. of 10% methanolic potassium hydroxide was heated under reflux for 15 min. The reaction mixture was then cooled and evaporated to dryness under reduced pressure. The pale yellow residue was dissolved in 900 ml. of water and the cooled solution was acidified to about pH 4.5 by the addition of 1200 ml. of a saturated solution of dihydrogen sodium phosphate. The resulting colorless precipitate was filtered, washed with water and dried. Crystallization from chloroform–ether gave 9.95 g. of product, m.p. 218.5–220.5°. A further 3.29 g. (m.p. 216–218°) was recovered from the mother liquors (total yield, 94.5%). Crystallization from chloroform–ether gave the analytical sample, m.p. 218–220.5°, $[\alpha]^{26}D$ + 1° (*c*, 1.00), λ_{max}^{KBr} 2.99, 5.73 and 5.91 μ.

Anal. Calcd. for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.70; H, 7.58.

Treatment of the above acid (II) in the usual manner with an excess diazomethane in ether gave the methyl ester (I), m.p. 193–197.5°. The melting point was undepressed upon admixture with the authentic sample.

3-Cyclic Ethylene Acetal of 17α-Acetoxy-3,11-dioxo-4-etiocholenic Acid (III).—To a solution of 13.14 g. of II in 27 ml. of anhydrous pyridine was added 9.5 ml. of freshly distilled acetic anhydride, the temperature of the mixture being kept below 30° by external cooling. The reaction mixture was then allowed to stand overnight at room temperature and was finally heated at 50° for 90 min. It was then evaporated to dryness in a vacuum. The residue was taken up in ether–methylene chloride (2.5:1) and was washed 3 times with water. The combined organic layer was dried (Na_2SO_4) and concentrated to dryness under reduced pressure. The residue was crystallized from methylene chloride–ether to give 13.23 g. of III, m.p. 217.5–220.5°. A further 0.58 g. (m.p. 216.5–218°) was recovered from the mother liquors (total yield, 95%). Crystallization from methylene chloride–ether gave the analytical sample, m.p. 218.5–220°, $[\alpha]^{26}D$ −38° (*c*, 0.672), λ_{max}^{KBr} 5.77, 5.85 and 7.95 μ.

Anal. Calcd. for $C_{24}H_{32}O_7$: C, 66.65; H, 7.46. Found: C, 66.87; H, 7.67.

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(5) We are indebted to Dr. A. Boris of our Pharmacology Department for carrying out these experiments.

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3-Cyclic Ethylene Acetal of 17α-Hydroxy-3,11-dioxo-4-etiocholenohydroxamic Acid (IV).—A stock solution of hydroxylamine was prepared: to a solution of 13.90 g. of hydroxylamine hydrochloride in 140 ml. of methanol was added portionwise a solution of sodium methoxide prepared from 4.6 g. of sodium and 100 ml. of methanol. The resulting mixture was cooled briefly and filtered from the precipitated sodium chloride. The ketal I (29.0 g.) was dissolved in 450 ml. of hot ethanol and then cooled to room temperature. A solution of sodium methoxide (prepared from 3.45 g. of sodium in 75 ml. of methanol) was added, and then 200 ml. of hydroxylamine stock solution (prepared as described above). The reaction mixture was stirred at room temperature overnight and concentrated to dryness under reduced pressure. The residue was dissolved in 2100 ml. of water and acidified to pH 4.5 by the addition of about 1200 ml. of saturated dihydrogen sodium phosphate solution. The resulting colorless precipitate was filtered, washed with water and dried. Crystallization from ethanol gave 19.6 g. (67.5% yield) of pure IV, m.p. 222–223° dec., $[\alpha]^{25}D$ +21° (*c*, 1.06), λ_{max}^{KBr} 2.86, 3.0, 3.05, 5.88 and 6.01 μ. The compound gave a strong purple coloration with ferric chloride.

Anal. Calcd. for $C_{22}H_{31}NO_6$: C, 65.16; H, 7.17; N, 3.45. Found: C, 65.23; H, 7.82; N, 3.66.

17α-Hydroxy-3,11-dioxo-4-etiocholenohydroxamic Acid (V).—To a solution of 7.0 g. of IV in 900 ml. of methanol was added 200 ml. of 4.5 *N* hydrochloric acid and the resulting solution was allowed to stand overnight at room temperature under nitrogen. It was concentrated to about 400 ml. under reduced pressure and then diluted with 1 l. of water. The resulting precipitate was filtered, washed with water and dried. Crystallization from ethanol gave 4.49 g. (72%) of V, m.p. 223.5–225.5° dec., $[\alpha]D$ +196° (*c*, 0.216), $\lambda_{max}^{C_2H_5OH}$ 238 mμ (ε 16,040), λ_{max}^{KBr} 2.95, 3.0, 5.87, 5.99 and 6.08 μ. The compound gave a strong purple coloration with ferric chloride.

Anal. Calcd. for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.56; H, 7.76; N, 3.94.

3-Cyclic Ethylene Acetal of O-Methyl-17α-hydroxy-3,11-dioxo-4-etiocholenohydroxamic Acid (VI).—Compound IV (810 mg.) was dissolved with some difficulty in 75 ml. of hot ethanol, and the solution was then concentrated to about 25 ml. by distillation. The resulting solution, cooled to room temperature, was treated with a 2 ml. aliquot of sodium ethoxide solution (2.5 g. of sodium in 100 ml. of ethanol) and then 0.16 ml. of methyl iodide. The reaction mixture was allowed to stand overnight at room temperature and was concentrated to dryness under reduced pressure. The residue was dissolved in ether–methylene chloride (3:1), the solution washed with water, dried (Na_2SO_4) and evaporated to dryness. Crystallization of the residue from ethanol gave 428 mg. (51%) of VI, m.p. 226–227° dec. Further crystallization from ethanol gave an analytical sample, m.p. 230–231° dec., $[\alpha]^{25}D$ +2° (*c*, 0.352), λ_{max}^{KBr} 2.95 and 5.87 μ (broad). The compound gave no coloration on treatment with ferric chloride.

Anal. Calcd. for $C_{23}H_{33}NO_6$: C, 65.85; H, 7.93; N, 3.34. Found: C, 65.86; H, 8.14; N, 3.39.

O-Methyl-17α-hydroxy-3,11-dioxo-4-etiocholenohydroxamic Acid (VII). (a) By Hydrolysis of the Ketal VI.—To a solution of 400 mg. of the ketal VI in 52 ml. of methanol was added 11.5 ml. of 4.5 *N* hydrochloric acid and the resulting mixture was allowed to stand overnight at room temperature under nitrogen. It was then concentrated to about 10 ml. under reduced pressure and diluted with 75 ml. of water. The solution was saturated with ammonium chloride and extracted with ether–methylene chloride (3:1); the extracts were washed with brine, dried (Na_2SO_4) and evaporated to dryness. Crystallization of the residue from methanol gave 187 mg. (52%) of VII, m. p. 219.5–222°. Crystallization from methanol gave an analytical sample, m.p. 224–225.5° dec., $[\alpha]^{25}D$ +166° (*c*, 1.06), $\lambda_{max}^{C_2H_5OH}$ 238 mμ (ε 15,700), λ_{max}^{KBr} 2.84, 3.05, 5.86, 5.91 and 6.02 μ. The compound gave no coloration with ferric chloride.

Anal. Calcd. for $C_{21}H_{29}NO_5$: C, 67.18; H, 7.79; N, 3.73. Found: C, 67.22; H, 7.65; N, 3.84.

(b) By Alkylation of V.—To a suspension of 1.80 g. of V in 36 ml. of anhydrous ethanol was added a 3.60 ml. aliquot of sodium ethoxide solution (3.40 g. of sodium in 100 ml. of ethanol). To this cooled pale yellow solution was added 3.0 ml. of methyl iodide and the reaction mixture was allowed to stand overnight at room temperature under nitrogen. The solvent now was removed under reduced pressure, the residue dissolved in methylene chloride, the solution washed with water, dried (Na_2SO_4) and evaporated to dryness. The residue was crystallized from methanol to give 1.52 g. (81%) of VII, m.p. 224–226.5° dec. The melting point was undepressed upon admixture with the sample prepared by method (a).

Acknowledgment.—We are indebted to Dr. A. Steyermark and his staff for the micro analyses, and to Dr. A. Motchane, Mr. S. Traiman and Dr. V. Toome for the infrared and ultraviolet spectra.

Steroids and Related Products. XVIII.[1] The Synthesis of 11β,12α-Dibromoprogesterone[2]

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The recent finding that 9,11-dihalogenated derivatives of steroid hormones exhibit interesting biological activities[4–6] seemed to call for an investigation of the effect of dihalogenation in positions 11 and 12 on hormonal potency. We were attracted toward this problem not only because of our interest in the effects of halogenation on the biological activities of steroid hormones[7a–d] but also because our laboratory has developed an efficient method for the preparation of 11,12-unsaturated steroids[8,9a,b] which represent suitable starting materials for the synthesis of 11,12-dihalogenated derivatives.[10]

As a first representative of 11,12-dihalogenated steroid hormones of the progesterone-corticoid group, we synthesized 11,12-dibromoprogesterone (VII), using the readily available 11-pregnene-3,20-dione (I)[8,9b,11a–c] as starting material.

The unsaturated diketone I was transformed with ethylene glycol and selenium dioxide[12a,b] to the crystalline 3-monoethylenedioxy derivative II, previously obtained in this laboratory, as an intermediate, in the amorphous state.[9b] Bromination in chloroform at low temperature, with one molecular equivalent of bromine,

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(2) The results reported in this paper were presented before the 5th Annual Meeting of the Canadian Federation of Biological Societies, Quebec, June, 1962 [*cf. Proc. Can. Fed. Biol. Soc.*, **5**, 26 (1962)].

(3) Correspondence should be addressed to this author.

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(10) We sincerely thank Dr. D. Gould and his colleagues of the Schering Corporation, Bloomfield, N. J., for informing us, prior to publication, of the activities of their 9,11-dihalo steroids.

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(12) Compare (a) E. P. Oliveto, H. Q. Smith, C. Gerold, R. Rausser, and E. B. Hershberg, *J. Am. Chem. Soc.*, **78**, 1414 (1956); (b) E. P. Oliveto, C. Gerold, and E. B. Hershberg, *ibid.*, **76**, 6113 (1954).