Ring-D-Bridged Steroid Analogs. II.[1] 14α,17α-Etheno-16α-carbomethoxypregn-4-ene-3,20-dione[2]

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Diels–Alder addition of methyl acrylate to 3β-acetoxy-20-keto-5,14,16-pregnatriene (I) afforded an adduct, IIa, which has been transformed into 14α,17α-etheno-16α-carbomethoxypregn-4-ene-3,20-dione (III). Synthesis of III has also been achieved by Diels–Alder additions of methyl acrylate to 4,14,16-pregnatriene-3,20-dione. Although III is inactive in the modified Clauberg assay, it appears capable of enhancing the activity of progesterone in that test.

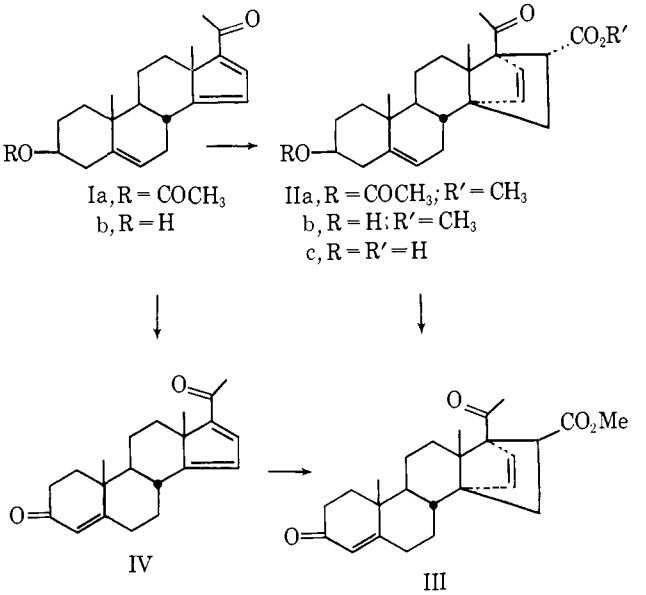
Many steroid hormone analogs bearing 17α-alkyl or 17α-O-acyl groups are known to be biologically active.[4] As the 17 substituents in these compounds are, in general, capable of free rotation, it seemed of interest to determine the effect, on biological activity, of restricting the conformational freedom of the 17α group. Molecular models show that steroid analogs, which bear two-atom bridges between the 14α and 17α positions, are geometrically similar to one of the rotomers of 17α-substituted steroids. We therefore decided to determine the effect of such two-atom bridges on the biological activity of various hormone analogs.

Recently, 3β-acetoxy-17-cyano-5,14,16-androstatriene was demonstrated to undergo the Diels–Alder reaction with a variety of dienophiles.[1] Difficulties which we encountered in the attempted conversion of these adducts to analogs of progesterone caused us to abandon that path in favor of one involving Diels–Alder addition to dienes more closely related to the final product.

Chemistry.—Heating 3β-acetoxy-20-keto-5,14,16-pregnatriene[5] with an excess of methyl acrylate at 120° for 165 hr resulted in the formation of the Diels–Alder adduct IIa in 82% yield. Selective hydrolysis of the acetate group of IIa readily afforded hydroxy compound IIb. Oxidation[6,7] of IIb afforded the progesterone analog III.

Hydrolysis of the acetate group of Ia was followed by oxidation[7] to afford 4,14,16-pregnatriene-3,20-dione (IV). Diels–Alder addition of methyl acrylate to IV provided a second path to 14α,17α-etheno-16α-carbomethoxypregn-4-ene-3,20-dione (III). The stereochemistry of the above adducts is tentatively assigned on the basis of analogies previously cited.[1]

Biological Activity.—Assuming our assignment of stereochemistry to be correct, 14α,17α-etheno-16α-carbomethoxypregn-4-ene-3,20-dione (III) may be regarded as a close analog of 16α-carbomethoxyprogesterone. Although 16α-carbomethoxy-,[8,9] 16α-carboxy-,[8,9] and 16α-cyanoprogesterone[8] have been synthesized by several research groups, progestational activity has not been claimed for any of them.[10] Despite this, we believed it worthwhile to test III for progestational and antiprogestational activity.



As shown in Table I, subcutaneous injections of up to 20 mg of III failed to elicit any response in the modified Clauberg assay.[11] An attempt was then made to detect possible antiprogestational activity for III, by administering it together with progesterone. However, as shown in Table I, when II was administered in a dose 6–25 times that of progesterone, the activity of the progesterone, in the Clauberg test, was enhanced. The latter effect appears to diminish with *increasing* dose ratios of III:progesterone until, at a dose ratio of 50, III does appear to weakly antagonize the effect of progesterone.

These results may be rationalized by assuming that III, or its metabolic degradation products, may be able to block both the enzymic degradation of progesterone and the action of progesterone at the site responsible for the effects monitored by the Clauberg assay. If the first effect is stronger than the second, low dose ratios of III:progesterone should enhance the activity of progesterone, while high dose ratios should repress

(1) Part I: A. J. Solo, H. S. Sachdev, and S. S. H. Gilani, *J. Org. Chem.*, **30**, 769 (1965).

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(3) To whom inquiries regarding this work should be addressed.

(4) N. Applezweig, "Steroid Drugs," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 313–320, 337–344.

(5) A. J. Solo and B. Singh, *J. Org. Chem.*, **30**, 1658 (1935).

(6) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

(7) C. Djerassi, *Org. Reactions*, **6**, 207 (1951).

(8) J. Romo, *Tetrahedron*, **3**, 37 (1958).

(9) B. Ellis, V. Petrow, and D. Wedlake, *J. Chem. Soc.*, 3748 (1958).

(10) A claim of selective anticortisone activity has been advanced for 16α-cyanoprogesterone: R. H. Mazur, U. S. Patent 2,817,671 (Dec 24, 1957); *Chem. Abstr.*, **52**, 8220 (1958).

(11) Biological testing was performed at the Endocrine Laboratory, Madison, Wis.

TABLE I

PROGESTATIONAL ACTIVITY IN A MODIFIED CLAUBERG ASSAY BY SUBCUTANEOUS INJECTION[a]

Material administered	Total dose, mg: Progesterone	Total dose, mg: Test compd	No. of rabbits	III: Progesterone	Response	Response relative to control
Progesterone	0.2		2		1.5+	
	0.8		3		3.7+	
	1.0		2		2.8+	
III		1	2		0.0	
		5	2		0.0	
		20	2		0.0	
III and progesterone	0.2	5	2	25	2.2+	+0.7
	0.2	10	2	50	1.2+	−0.3
	0.8	5	2	6.25	4.0+[b]	+0.3[c]
	0.8	10	2	12.5	4.0+[b]	+0.3[c]
	0.8	20	2	25	4.0+[b]	+0.3[c]
	1.0	10	2	10	3.8+	+1.0

[a] All tests at a given total dose level of progesterone were run concurrently. The experiments at different total dose levels of progesterone were run, as separate experiments, at different times. [b] Maximum possible response in this assay is 4.0+. [c] These values should be considered as minimal because of *b*.

it, as observed. An attempt to test this hypothesis is underway in this laboratory, and an effort is being made to synthesize progestationally active ring-D-bridged analogs of progesterone.

Experimental Section[12]

3β-Hydroxy-20-keto-5,14,16-pregnatriene (Ib).—A mixture of 0.519 g of 3β-acetoxy-20-keto-5,14,16-pregnatriene (mp 159–160°), 0.523 g of KOH, 10 ml of *t*-butyl alcohol, and 0.6 ml of water was stirred at room temperature for 25 hr. The mixture was then partitioned between chloroform and water. After the $CHCl_3$ layer had been dried ($MgSO_4$), the chloroform was distilled under reduced pressure. The residue was crystallized from acetone to give Ib in a yield of 0.452 g (91%), as white rods, mp 191–193°, λ_{max}^{EtOH} 310 mμ (ϵ_{max} 12,600) [lit.[13] mp 186–187°, λ_{max} 307 mμ (log ϵ_{max} 4.23)], ν^{Nujol} 3500 and 1635 cm^{-1}. The nmr spectrum showed a singlet at δ 2.33 (21-CH_3) and peaks at δ 5.45, 6.05, and 7.27 (doublet, J = 2 cps) corresponding to the 6, 15, and 16 protons, respectively.

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.57; H, 9.23.

Adduct IIa of Ia with Methyl Acrylate.—A mixture of 1.947 g of 3β-acetoxy-5,14,16-pregnatrien-20-one (Ia), 3.0 ml of freshly distilled methyl acrylate, and 15 mg of hydroquinone was sealed in a glass tube under reduced pressure. After the reactants had been heated at 120° for 165 hr, the mixture was cooled to room temperature, the tube was opened, and the volatile matter was removed by distillation under reduced pressure at 100°. The residue was purified by filtration through a column of 50 g of Merck acid-washed alumina, using benzene containing up to 10% of ethyl acetate as eluent. The adduct IIa was then obtained from acetone in a yield of 1.984 g (82%) as white rods: mp 164–165°; ν^{CCl_4} 1740, 1706, 1242 cm^{-1}. The nmr spectrum showed singlets at δ 2.02 (acetate), 2.25 (21-CH_3), and 3.59 (CH_3 of ester), and peaks in the vinyl proton region at 5.44 (multiplet), 6.18 (doublet, J = 6 cps), and 6.25 (doublet, J = 6 cps).

Anal. Calcd for $C_{27}H_{36}O_5$: C, 73.61; H, 8.24. Found: C, 73.80; H, 8.40.

Selective Hydrolysis of Adduct IIa.—A mixture of 2.63 g of IIa, 2.48 g of KOH, 55.0 ml of methanol, and 5.0 ml of water was stirred at room temperature for 25 hr. After the mixture had been concentrated under reduced pressure, it was partitioned between water and ether. After the organic phase had been dried ($MgSO_4$), it was filtered and the ether was distilled. The residue was chromatographed on a column of 55.0 g of Merck acid-washed alumina. The column was first developed with 200 ml of benzene containing 5% ethyl acetate. A total of 229 mg of starting material (IIa) was then eluted by passage of 100 ml of 10% ethyl acetate in benzene followed by 100 ml of 15% ethyl acetate in benzene. Passage of another 50 ml of 15% ethyl acetate in benzene through the column was followed by 100 ml of 20% ethyl acetate in benzene to afford material which crystallized from acetone to give alcohol IIb, in a yield of 1.88 g, as small white rods: mp 176–178°; ν^{Nujol} 3360, 1735, 1695, 1647, 1618 cm^{-1}. The nmr spectrum showed singlets at δ 2.25 (21-CH_3) and 3.59 (ester CH_3), and peaks in the vinyl proton region at 5.40 (multiplet), 6.12 (doublet, J = 6 cps), and 6.26 (doublet, J = 6 cps).

Anal. Calcd for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 75.14; H, 8.70.

The aqueous layer was acidified with HCl and then extracted with ether. On standard work-up of the ether layer, a residue was obtained which crystallized from acetone to give hydroxy acid IIc as white rods: mp 233–234°; ν^{Nujol} 3490, 2740, 2618, 1721, 1704 cm^{-1}.

Anal. Calcd for $C_{23}H_{32}O_4$: C, 75.34; H, 8.60. Found: C, 75.14; H, 8.71.

14α,17α-Etheno-16α-carbomethoxypregn-4-ene-3,20-dione (III). A. By Jones Oxidation[6] of IIb.—A solution of 107 mg of hydroxy ester IIb in 25 ml of acetone (freshly distilled from $KMnO_4$) was cooled in an ice bath for 30 min. Then, 0.0016 equiv of Jones Reagent[6] was added, dropwise with stirring. After the mixture had stirred in an ice bath for 1 hr, several drops of ethanol were added to destroy any unreacted chromic acid. The mixture was then partitioned between chloroform and distilled water. The organic phase was washed wih aqueous HCl and then with water. Since nmr evidence indicated that the double bond was still at the 5,6 position, the chloroform solution was stirred with several drops of aqueous HCl for 4 hr. The solution was then washed with water and dried ($MgSO_4$). After the $CHCl_3$ had been distilled under reduced pressure, the residue was crystallized from acetone–hexane to afford 68 mg of III (63% yield) as white plates, mp 169–170°. Recrystallization from acetone afforded the analytical sample: mp 169.5–170.5°; ν^{CCl_4} 1737, 1704, 1675, 1616 cm^{-1}. The nmr spectrum had singlets at δ 2.25 (21-CH_3) and 3.60 (ester CH_3) and peaks in the vinyl proton region at 5.75 and 6.17.

Anal. Calcd for $C_{25}H_{32}O_4$: C, 75.73; H, 8.13. Found: C, 75.58; H, 7.96.

B. By Oppenauer Oxidation[7] of IIb.—A solution of 948 mg of IIb, 6.0 ml of cyclohexanone, and 180 ml of toluene was azeotroped under a Dean–Stark head for 1.5 hr. After the solution had been cooled and 1.125 g of aluminum isopropoxide added, reflux was resumed for 2.5 hr. The toluene was then distilled under reduced pressure. The residue was partitioned between $CHCl_3$ and aqueous HCl. The organic phase was dried and then evaporated to dryness under vacuum. The residue was heated on a steam bath under reduced pressure for 30 min and was then filtered through a column of 25 g of Merck acid-washed alumina. Condensation products of cyclohexanone were eluted by hexane and then by benzene. Finally benzene eluted material which

(12) 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.

(13) P. A. Plattner, H. Heusser, and A. Segre, *Helv. Chim. Acta*, **31**, 249 (1948).

crystallized from acetone–hexane to afford 0.683 g (71.5% yield) of white crystals: mp 169–170°; identical, by mixture melting point and nmr comparison, with III prepared above.

C. By Diels–Alder Addition of Methyl Acrylate to IV.—A mixture of 0.311 g of IV, 1.3 ml of freshly distilled methyl acrylate, and 10 mg of hydroquinone was sealed in a glass tube, under reduced pressure. After the tube had been heated at 120° for 96 hr, it was cooled and then opened. The contents were concentrated under reduced pressure. The residue was chromatographed over 20 g of Merck acid-washed alumina. Elution with benzene–ethyl acetate afforded 0.319 g of material which crystallized from acetone–hexane to afford 0.288 g of white flakes, mp 171–172°. The identity of this material with the 14α,17α-etheno-16α-carbomethoxypregn-4-ene-3,20-dione obtained in A was demonstrated by nmr spectroscopy and by a mixture melting point determination.

4,14,16-Pregnatriene-3,20-dione (IV).—A mixture of 1.93 g of 5,14,16-pregnatrien-3β-ol-20-one, 13.0 ml of cyclohexanone, and 300 ml of toluene was dried by refluxing under a Dean–Stark head until no further water separated (4 hr). The mixture was then cooled to room temperature, and 2.03 g of aluminum isopropoxide was added. The reactants were heated under reflux for 1 hr. After the toluene had been distilled under reduced pressure, the residue was partitioned between $CHCl_3$ and aqueous HCl. The chloroform solution was then dried ($MgSO_4$), filtered, and evaporated to dryness under reduced pressure. The residue, in benzene solution, was chromatographed over 210 g of Merck acid-washed alumina. Benzene (150 ml) eluted 200 mg of impurities followed by 334 mg of impure product. A solution (150 ml) of 5% ethyl acetate in benzene followed by 100 ml of 10% ethyl acetate in benzene then eluted 1.32 g of semisolid material which crystallized from acetone to afford 1.22 g of an acetone complex of IV as pale yellow crystals, mp 105–106°.

Anal. Calcd for $C_{21}H_{26}O_2 \cdot 0.5C_3H_6O$: C, 79.61; H, 8.61. Found: C, 79.72, 79.54; H, 8.53, 8.37.

The product was recrystallized from ethanol to afford an ethanol complex as pale yellow crystals: mp 114–115°; ν^{Nujol} 1669, 1647, 1629, 1618 cm^{-1}. The nmr spectrum had a singlet at 2.33 (21-CH_3) and peaks in the vinyl proton region at 5.80, 6.07, and 7.28 (doublet, J = 2 cps).

Anal. Calcd for $C_{21}H_{26}O_2 \cdot 0.5C_2H_6O$: C, 79.24; H, 8.77. Found: C, 79.47; H, 8.53.

Derivatives of Piperazine. XXXV.[1a] Synthesis of 2-Phenylpiperazine and Some Derivatives

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Three methods for the synthesis of 2-phenylpiperazine (**3**), two of them new, have been investigated. One method concerned the condensation of ethyl α-bromophenylacetate with ethylenediamine to form 3-oxo-2-phenylpiperazine (**4**) followed by hydride reduction to **3**. This method was superior to the condensation of styrene oxide with ethylenediamine, previously employed. The second method involved condensation of ethyl glycinate, cyanide, and benzaldehyde to ethyl N-(α-cyanobenzyl)glycinate (**5**), which was hydrolyzed to the amido ester **6**. The latter was cyclized by sodium hydride to 3,5-dioxo-2-phenylpiperazine (**7**) which was reduced to **3**. The 1-alkyl derivatives of **3** were obtained unambiguously by alkylation of 3-oxo-2-phenylpiperazine followed by hydride reduction. The 4-alkyl and 1,4-dialkyl derivatives were prepared by alkylation of **3**.

Of the very large number of derivatives of piperazine, many of which have been investigated for various pharmacological activities, relatively few C-substituted derivatives have been studied.[2] Aside from the 2,5-disubstituted piperazines obtained by dehydration of amino acids to diketopiperazines followed by reduction, the synthesis of C-substituted piperazines offers several difficulties.[3] The first synthesis of 2-phenylpiperazine (**3**) was reported in 1943[4]; no other synthesis or papers concerning this compound have appeared, although related keto derivatives and further C-substituted derivatives have been reported. The structure of **3**, since it contains the phenethylamine moiety of the sympathomimetic amines, should be of special interest to medicinal chemistry. We report here an improved synthesis of **3** and the synthesis of some N-alkyl and oxo derivatives, prepared for pharmacological evaluation.

The first method of synthesis of **3** consisted of the reaction of styrene oxide with excess ethylenediamine to form N-(β-hydroxy-β-phenethyl)ethylenediamine (**1**) which was catalytically cyclodehydrated at high pressure in the presence of Raney nickel. The adducts of styrene oxide and amines have been assumed to result from attack at the β-carbon of styrene oxide.[5] For the reaction of several amines with styrene oxide, the major but not exclusive product has been shown to result from attack at the less substituted carbon atom.[6] This method of synthesis of **3** was reinvestigated in an attempt to improve the yield, and data were obtained to support the structure previously assigned (without proof) to the styrene oxide–ethylenediamine adduct.

From the reaction of 1 mole of styrene oxide with 2 moles of ethylenediamine, the 1:1 adduct (**1**) was obtained in 60% yield based on styrene oxide. A 2:1 adduct (**2**) was also obtained, in 11% yield based on styrene oxide. The structures of **1** and **2** were based on elemental analyses, nmr spectral comparisons, and the absence of primary amine in **2** as shown by the Hinsberg test. The nmr spectrum of **1** showed the

(1) (a) Part XXXIV: C. B. Pollard, W. M. Lauter, and N. O. Nuessle, *J. Org. Chem.*, **24**, 764 (1959). (b) Communications regarding this paper should be addressed to the Department of Organic Chemical Research, Abbott Laboratories, North Chicago, Ill. 60064. (c) This paper was abstracted from the Ph.D. Dissertation, University of Florida, June 1962. (d) Deceased; formerly Professor of Chemistry, University of Florida.

(2) E. Jucker and E. Rissi, *Helv. Chim. Acta*, **45**, 2383 (1962).

(3) For example, the synthesis of N-phenylpiperazines from arylamines and diethanolamine hydrochloride could not be extended to the synthesis of C-substituted piperazines: J. P. Bain and C. B. Pollard, *J. Am. Chem. Soc.*, **61**, 2704 (1939).

(4) L. J. Kitchen, Ph.D. Dissertation, University of Florida, Feb. 1943; C. B. Pollard and L. J. Kitchen, U. S. Patent 2,400,022 (1946); *Chem. Abstr.*, **40**, 5074 (1946); L. J. Kitchen and C. B. Pollard, *J. Am. Chem. Soc.*, **69**, 854 (1947).

(5) W. S. Emerson, *ibid.*, **67**, 516 (1945).

(6) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).