The infrared spectra of the reduction products retained the indolic NH stretching frequencies and the ultraviolet spectra were similar to those of the parent lactams which were shown to have the indole chromophore.

Heating an ethanol solution of the amine with an excess of picric acid gave bright orange crystals of the picrate melting at 243–244° dec. after recrystallization from ethanol.

Anal. Calcd. for $C_{22}H_{23}N_5O_8$: C, 54.43; H, 4.77; N, 14.43. Found: C, 54.23; H, 4.84; N, 14.23.

The methiodide, prepared by refluxing the amine with an excess of methyl iodide in benzene for 5 min., was a colorless crystalline compound, melting at 267–268° after recrystallization from ethyl acetate–benzene.

Anal. Calcd. for $C_{17}H_{23}IN_2O$: C, 51.26; H, 5.82; N, 7.04. Found: C, 51.30; H, 6.11; N, 6.76.

N-β-(3-Indolyl)ethyl-2-phenyl-5-oxo-Δ²-pyrroline (IV, R_1 = H; R_2 = C_6H_5).—A mixture of 3.00 g. of tryptamine (0.019 mole), 3.45 g. of β-benzoylpropionic acid (0.020 mole), and 175 ml. of dry toluene was refluxed for 8 hr. in a flask fitted with a Dean–Stark water trap. Complete solution was attained after 5 hr. and 0.67 ml. of water (0.037 mole) had collected. After evaporating the solvent under reduced pressure, a red-yellow amorphous solid was obtained. Two recrystallizations from methanol gave 0.47 g. of yellow powder melting at 178–192°. Trituration with methanol gave a yellow powder melting at 197–200° dec. This material was shown to be present in at least 60% yield when column chromatography was used to separate the condensation product. The Ehrlich color test produced a deep red color, indicating the 2-position of the indole moiety is unsubstituted. The infrared spectrum showed major absorptions at 3300 (NH), 1680 (C=O), 1645 (enamine), and 698 cm.$^{-1}$ (aromatic).

Anal. Calcd. for $C_{20}H_{18}N_2O$: C, 79.44; H, 6.00; N, 9.26. Found: C, 79.57; H, 6.00; N, 9.25.

Acknowledgment.—The authors wish to express appreciation to Smith Kline and French Laboratories for a fellowship which supported part of this investigation, for a gift of 1,2,3,4-tetrahydro-1-oxo-6-methoxy-β-carboline, and for the pharmacological data.

A Carbocyclic Analog of Glyceraldehyde Dimer

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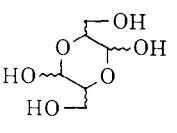
This note presents the synthesis of 2,5-dihydroxycyclohexane-1,4-dimethanol (**4**), a carbocyclic analog of racemic glyceraldehyde dimer (**1**) in which methylene groups replace the ring oxygen linkages. Due to complex side reactions the starting material, diethyl 2,5-diketohexahydroterephthalate (**2**), could not be reduced directly to **4** using lithium aluminum hydride. Catalytic reduction to the intermediate diol diester (**3**) was at first ineffective. If, however, **2** were freshly sublimed, reduction at 1 atm. using platinum oxide in methanol proceeded steadily and in 2 days the calculated amount of hydrogen was utilized. Crystallization from carbon tetrachloride gave **3** which, because of the general course of catalytic reduction over platinum,[1] is given the all *cis* configuration illustrated. Support for this stereochemistry was derived also from the n.m.r. spectrum of this substance as a 10 mole % solution in dimethyl sulfoxide[2] which shows two nonequivalent secondary OH groups (a doublet at δ = 4.72 p.p.m., 1.5-c.p.s. splitting, and a doublet at δ = 4.80 p.p.m., 3.5-c.p.s. splitting), a result consistent with a chair form of the all *cis* isomer.



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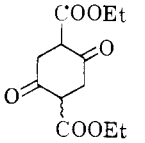

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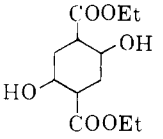

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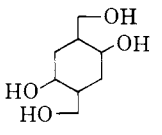

4

This diol diester also resisted reduction by lithium aluminum hydride. It was hoped that a reagent with only one replaceable hydride atom would have less complexing tendencies and permit reduction of the two carbethoxy groups of **3**. Lithium tri-*t*-butoxyaluminohydride[3] proved effective for this purpose and, although the product was chelated, the chelate was cleavable by mild treatment with dilute hydrofluoric acid. The tetrol **4**, after evaporative distillation and recrystallization, was isolated in 50% yield. Epimerization of **3** by the lithium tri-*t*-butoxyaluminohydride could have produced three optically inactive tetrols. Despite examination of the mother liquors by thin layer chromatography, no other isomer was isolated, suggesting that the steric relations of **3** had been retained. Support for this configuration was found in the n.m.r. spectrum of **4** as a 10 mole % solution in dimethyl sulfoxide. Two nonequivalent primary alcohol triplets were found at δ = 4.18 (4-c.p.s. splitting) and 4.34 p.p.m. (2.5-c.p.s. splitting). Nonequivalent secondary alcohol protons gave signals at δ = 4.46 and 4.53 p.p.m. All of these signals were removed on exchange with deuterium oxide. This pattern is compatible with a chair conformation of **4** in which neither the primary nor the secondary alcohol groups are equivalent. (Sirupy D- and crystalline DL-glyceraldehyde do not give resolved OH proton signals when determined under these conditions.)

Since DL-glyceraldehyde dimer has been shown to have biological activity (inhibition of glycogen phosphorolysis[4]), it became desirable to evaluate **4**, a close structural analog of this dimer, for antitumor activity. In tests conducted by the Cancer Chemotherapy National Screening Center, **4** was nontoxic and inactive at a dose level of 200 mg./kg. against lymphoid leukemia L1210 and P1798 lymphosarcoma and also against Dunning ascites leukemia at 100 mg./kg. It was rated inactive against KB cell culture in which its ED_{50} was greater than 1000 γ/ml.

Experimental[5]

1,4-Dicarbethoxy-2,5-dihydroxycyclohexane (3).—Freshly sublimed [125° (20 μ)] **2** (5.8 g.) was mixed with 1.18 g. of plati-

(1) J-F. Sauvage, R. H. Baker, and A. S. Hussey, *J. Am. Chem. Soc.*, **82**, 6090 (1960), and references cited therein.

(2) O. L. Chapman and R. W. King, *ibid.*, **86**, 1256 (1964).

(3) H. C. Brown and R. F. McFarlin [*ibid.*, **80**, 5372 (1958)] report no reduction of esters with the reagent but this was under much milder conditions.

(4) H. Lehmann and J. Needham, *Enzymologia*, **5**, 95 (1938).

(5) Melting points were taken in capillaries using a Hershberg apparatus and are corrected. N.m.r. spectra were determined by Mrs. Josephine Goodwin on a Varian A-60 instrument using tetramethylsilane as internal reference. Microanalyses were performed by Miss Paula M. Parisius under the direction of Dr. William C. Alford.

mum dioxide and 200 ml. of methanol. After shaking with hydrogen at room temperature and 1 atm. for 48 hr., the calculated amount of hydrogen was consumed. Filtration, evaporation of the filtrate, and crystallization from CCl_4 gave 3.61 g. (61%) of white solid, m.p. 84–88°. The analytical sample was recrystallized from CCl_4 and dried at 45° (30 μ), m.p. 98–98.5°.

Anal. Calcd. for $C_{12}H_{20}O_6$: C, 55.37; H, 7.75. Found: C, 55.39; H, 8.06.

2,5-Dihydroxycyclohexane-1,4-dimethanol (4).—A mixture of 28.0 g. of lithium tri-*t*-butoxyaluminohydride, 2.08 g. of vacuum-dried 1,4-dicarbethoxy-2,5-dihydroxycyclohexane, and 88 ml. of tetrahydrofuran was refluxed with stirring for 22 hr. After cooling, there was added 36 ml. of water (hydrogen evolution), 200 ml. of MeOH, 32.4 g. of NaF, and gradually, with ice bath cooling so that the temperature did not exceed 20° during the addition, 36.6 ml. of 38% HCl. The resulting slurry was filtered and the filtrate was evaporated. The filtration residue was evaporatively distilled at 210° (15 μ) overnight. Crystallization of the distillate from methanol-acetone gave 0.70 g., m.p. 141–142°. The analytical sample was crystallized from isopropyl alcohol and dried at 100° (50 μ).

Anal. Calcd. for $C_8H_{16}O_4$: C, 54.53; H, 9.15. Found: C, 54.36; H, 8.85.

Acknowledgment.—The author thanks Dr. Howard W. Bond of the Cancer Chemotherapy National Screening Center for arranging the biological testing.

The Preparation and Some Biological Properties of 17α-Ethyl-17β-methyl-$\Delta^{4,13}$-gonadien-3-one

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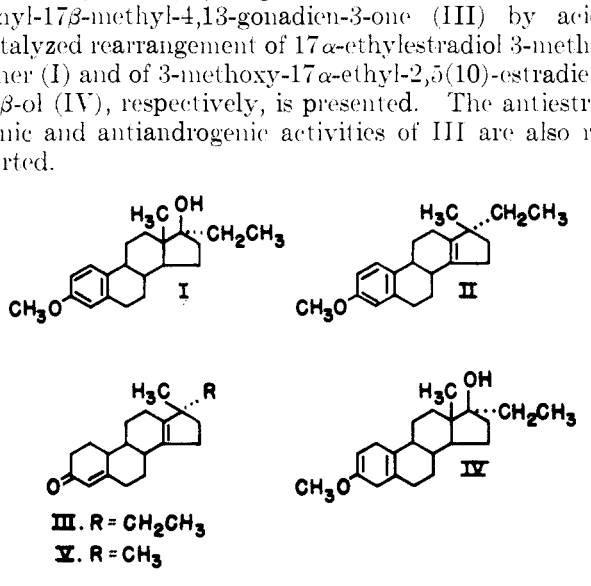
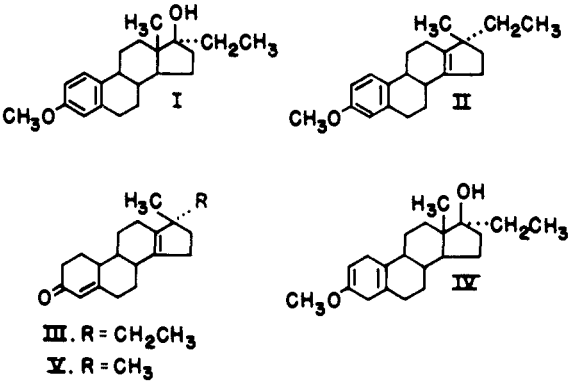
The preparation, proof of structure, and antiestrogenic and antiandrogenic activities of the novel 17,17-dimethyl-4,13-gonadien-3-one (V) have been described.[1] Since this suggested competitive inhibition at the site of action with the parent hormones, it was of interest to examine the biological effect of varying the 17α-substituent. The preparation of 3-methoxy-17α-ethyl-17β-methyl-1,3,5(10),13-gonatetraene (II) and 17α-ethyl-17β-methyl-4,13-gonadien-3-one (III) by acid-catalyzed rearrangement of 17α-ethylestradiol 3-methyl ether (I) and of 3-methoxy-17α-ethyl-2,5(10)-estradien-17β-ol (IV), respectively, is presented. The antiestrogenic and antiandrogenic activities of III are also reported.



(1) R. Kirdani, R. I. Dorfman, and W. R. Nes, *Steroids* **1**, 219 (1963).



Proof of structure for the *gem*-ethylmethyl compounds reported in the present work follows: (a) by analogy to the preparation of the *gem*-dimethyl analogs,[1] (b) from the ultraviolet and infrared spectra indicating that ring A is intact in both the estrogen methyl ether and the Δ^4-3-ketone, and (c) from the n.m.r. spectra in which strong singlets due to the methyl groups at 17 are present at τ 9.00 close to the multiplets of the 17α-groups.

Experimental

Melting points are uncorrected and were taken on a Fisher-Johns melting point apparatus. Ultraviolet spectra were determined on a Cary Model 14 recording spectrophotometer. Infrared spectra were determined on a Perkin-Elmer Infracord and a Beckman IR-7 infrared spectrophotometer. Rotations were measured in a Hilger Mark III standard polarimeter. N.m.r. spectra were determined on a Varian Associates instrument Model V 4302. Combustion analyses were performed by Schwarzkopf Microanalytical Laboratories. 17α-Ethylestradiol 3-methyl ether was purchased from Steraloids, Inc.

17α-Ethyl-3-methoxy-17β-methyl-1,3,5(10),13-gonatetraene (II).—A solution of 500 mg. of 17α-ethylestradiol 3-methyl ether in 50 ml. of 1 *M* HCl in methanol was refluxed for 18 hr. The mixture was then diluted with water and extracted with ether, and the ether extract was washed with saturated $NaHCO_3$ and dried (Na_2SO_4). The residue remaining on evaporation of solvent was applied in hexane to a column of silica gel (50 g., Grace, Davidson Chemical). After washing the column with 300 ml. of hexane the product (400 mg.) was eluted with 20% benzene in hexane. The analytical sample melted at 55–56°; λ_{max}^{EtOH} 287 mμ (ϵ 1975) and 278 mμ (ϵ 2180); $\lambda_{max}^{CS_2}$ 1272, 1240, and 1050 cm.$^{-1}$; n.m.r. maxima (τ): 2.74 and 3.38 (multiplets, aromatic protons), 6.29 (OCH_3), 8.71 (quartet, CH_2CH_3), 9.04 (17β-CH_3), and 9.23 (triplet, 17α-CH_2CH_3, J = 7.0 c.p.s.); $[\alpha]D$ −38° (chloroform).

Anal. Calcd. for $C_{21}H_{28}O$: C, 85.08; H, 9.52. Found: C, 84.92; H, 9.57.

17α-Ethyl-3-methoxy-2,5(10)-estradien-17β-ol (IV) was prepared by Birch reduction of 17α-ethylestradiol 3-methyl ether as described by Colton, *et al.*[2] The melting point was 126.5–128° (lit.[2] m.p. 126–128°); no selective absorption in the ultraviolet; $\lambda_{max}^{CS_2}$ 3575, 1660, and 1220 cm.$^{-1}$.

17α-Ethyl-17β-methyl-4,13-gonadien-3-one (III).—IV was treated as described above for the preparation of II. The product was chromatographed on silica gel, eluted with 2% ether in benzene, and crystallized twice from aqueous methanol. The yield from 17α-ethylestradiol 3-methyl ether for the two steps was 35%. The analytical sample melted at 82–83°; λ_{max}^{EtOH} 239 mμ (ϵ 15,900); $\lambda_{max}^{CS_2}$ 1675 and 1617 cm.$^{-1}$; peaks in the n.m.r. spectrum in τ values: 4.12 (C-4 proton), 8.63–8.88 (quartet, CH_2CH_3), 9.03 (17β-CH_3), and 9.25 (triplet, 17α-CH_2CH_3, J = 6.7 c.p.s.); $[\alpha]D$ −52° (chloroform).

Anal. Calcd. for $C_{20}H_{28}O$: C, 84.45; H, 9.92. Found: C, 84.67; H, 9.86.

(2) F. B. Colton, L. N. Nysted, B. Riegel, and A. L. Raymond, *J. Am. Chem. Soc.*, **79**, 1123 (1957).