D-Mannitol hexanitrate was treated with either triethylamine or N,N-dimethylaniline following the Hayward pyridine denitration technique.[5] Triethylamine effected a vigorous reaction that teminated in a fire. Dilution of the system with acetonitrile was employed to moderate the reaction but no crystalline products were obtained. In contrast, N,N-dimethylaniline diluted with acetonitrile afforded D-mannitol hexanitrate in 60% yield as the only crystalline product. In view of the diversity of the two bases (above) which effect the denitration in high yield, these results are surprising.

Solutions of either 3-*O*-allyl- or 3-*O*-propionyl-D-mannitol in ethanol containing twice their weight of *p*-toluenesulfonic acid were stirred at room temperature for 20 hr. Cooling and adding water in each case afforded the unchanged starting material quantitatively.

COLUMBUS 10, OHIO

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

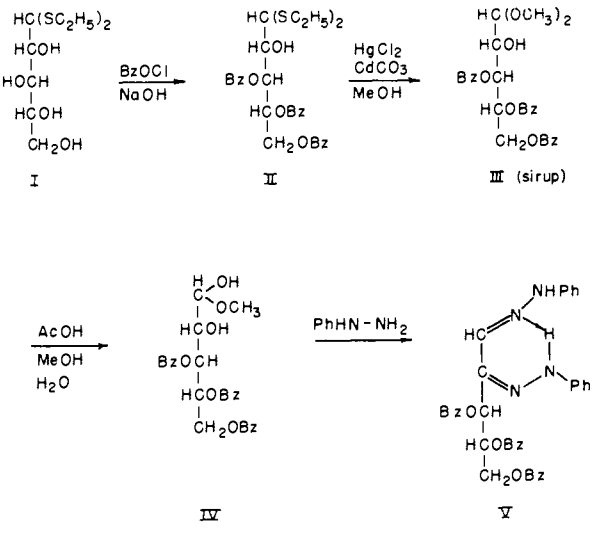
3,4,5-Tri-*O*-benzoyl-D-xylose Dimethyl Acetal[1]

BY M. L. WOLFROM AND WALTER VON BEBENBURG

RECEIVED MAY 28, 1959

D-Xylose diethyl dithioacetal was partially benzoylated to form a tribenzoate followed by successive conversion of the diethyl dithioacetal to the dimethyl acetal tribenzoate and the methyl hemiacetal tribenzoate. The latter substance produced a phenylosazone, without loss of benzoyl groups, identical with the product of benzoylation of D-xylose phenylosazone, indicating that carbon two in the members of this series was unbenzoylated.

3,4,5,6-Tetra-*O*-benzoyl-D-glucose diethyl dithioacetal[2] has been prepared by the partial benzoylation of D-glucose diethyl dithioacetal. The free hydroxyl group was substituted by a thioethoxyl group[3] which after demercaptalation and debenzoylation[4] produced D-*arabino*-hexose (D-glucose) phenylosazone indicating that the unsubstituted hydroxyl group was on carbon two. Since the pentose D-xylose possesses the same configuration as D-glucose for the two centers below



Bz = benzoyl; Ph = phenyl

the carbonyl group, it was considered that the extension of this reaction to D-xylose would be feasible. D-Xylose diethyl dithioacetal (I) was partially benzoylated to produce 3,4,5-tri-*O*-benzoyl-D-xylose diethyl dithioacetal (II). The diethyl dithioacetal (II) was converted[5] successively to the sirupy dimethyl acetal III, the crystalline methyl hemiacetal IV and the crystalline phenylosazone without loss of a benzoyl group, indicating that the free hydroxyl group is at carbon two.

Acknowledgment.—The counsel and assistance of Doctors F. Shafizadeh and A. Thompson is gratefully acknowledged.

Experimental

3,4,5-Tri-*O*-benzoyl-D-xylose Diethyl Dithioacetal (II).—D-Xylose diethyl dithioacetal[6] (I, 90 g., 0.35 mole) was dissolved at 0° in 1500 ml. of 2 *N* sodium hydroxide. A solution of 160 g. (1.15 mole) of benzoyl chloride in 600 ml. of chloroform was added portionwise with vigorous stirring and cooling in an ice–salt-bath so that the temperature did not exceed 10°. After the addition, stirring was continued for 30 min. The chloroform layer was washed several times with water and dried with anhydrous sodium sulfate. The chloroform was evaporated under reduced pressure and the sirupy residue was dissolved in 500 ml. of hot ethanol and 150 ml. of water added. Fine needles separated and after standing for 24 hr. at room temperature, the mixture had completely solidified. The compound was recrystallized thrice from ethanol–water; yield 58 g. (29%), m.p. 138–140°, $[\alpha]^{20}D$ +6° (*c* 3, chloroform).

Anal. Calcd. for $C_{30}H_{32}O_7S_2$: C, 63.34; H, 5.67; S, 11.28. Found: C, 63.27; H, 5.61; S, 11.38.

3,4,5-Tri-*O*-benzoyl-*aldehydo*-D-xylose Methyl Hemiacetal (IV).—3,4,5-Tri-*O*-benzoyl-D-xylose diethyl dithioacetal (II, 10 g., 0.176 mole) was dissolved in 120 ml. of dry methanol in which 25 g. of dry cadmium carbonate was suspended and the mixture was heated to boiling. A solution of 45 g. of mercuric chloride in 100 ml. of methanol was added in portions with vigorous stirring. The mixture was refluxed for 4 hr. with the occasional addition of small amounts of cadmium carbonate. The solution was filtered into a flask containing 5 g. of cadmium carbonate, and the filtrate was evaporated to dryness under reduced pressure. The residue was extracted several times with chloroform. The combined chloroform extract was washed with potassium iodide solution, and water, dried with sodium sulfate and evaporated under reduced pressure to a sirup. This colorless sirup contained no sulfur and failed to crystallize after six months. This sirupy 3,4,5-tri-*O*-benzoyl-D-xylose dimethyl acetal (III, 2 g.) was dissolved in 100 ml. of methanol to which 1 ml. of acetic acid and 10 ml. of water were added, and the solution refluxed for 3 hr. A 50-ml. portion of this solution was diluted with 30 ml. of water. After standing overnight, crystalline material separated and was recrystallized twice from methanol; yield 750 mg., m.p. 131°, $[\alpha]^{30}D$ + 24 → −18° (*c* 0.7, methanol, 42 hr.).

(1) Supported by Grant No. CY-3232 from the Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, Bethesda 14, Md.

(2) P. Brigl and H. Mühlschlegel, *Ber.*, **63**, 1551 (1930).

(3) P. Brigl, H. Mühlschlegel and R. Schinle, *ibid.*, **64**, 2921 (1931).

(4) P. Brigl and R. Schinle, *ibid.*, **65**, 1890 (1932).

(5) M. L. Wolfrom, L. J. Tanghe, R. W. George and S. W. Waisbrot, THIS JOURNAL, **60**, 132 (1938).

(6) M. L. Wolfrom, Mildred R. Newlin and E. E. Stahly, *ibid.*, **53** 4379 (1931).

Anal. Calcd. for $C_{27}H_{26}O_9$: C, 65.58; H, 5.30. Found: C, 65.68; H, 5.29.

3,4,5-Tri-*O*-benzoyl-D-*threo*-pentose Phenylosazone (V).—A 50-ml. portion of the solution resulting from boiling III with dilute acetic acid was further refluxed for 4 hr. with 1 ml. of freshly distilled phenylhydrazine. The fine yellow needles which formed were filtered and recrystallized twice from water–ethanol; yield 10 mg., m.p. 196°. The X-ray powder diffraction pattern was identical with that of a sample prepared by benzoylation of D-xylose phenylosazone. D-Xylose phenylosazone (1 g.) was suspended in a mixture of 10 ml. of pyridine and 10 ml. of chloroform and treated with 2.0 g. of benzoyl chloride for 24 hr. at room temperature. The solution was poured into water, the chloroform layer separated, washed with water, dried and evaporated to a sirup. It was crystallized from abs. ethanol; yield 2 g., dec. 176–186°, $[\alpha]^{20}D$ +5° (*c* 0.85, chloroform); X-ray powder diffraction data[7]: 11.87m, 10.85w, 6.19vw, 5.25vs(1), 4.56vw, 4.36m(3), 4.21s(2), 3.96m, 3.63vw, 3.49vw, 3.42vw, 3.08w.

Anal. Calcd. for $C_{33}H_{32}N_4O_6$: C, 71.23; H, 5.03; N, 8.76. Found: C, 71.23; H, 5.16; N, 8.93.

(7) Interplanar spacing, Å., CuKα radiation; intensity of lines estimated visually: s, strong; m, medium; w, weak; v, very; parenthetic numerals indicate three strongest lines; 1, strongest line.

COLUMBUS 10, OHIO

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WISCONSIN]

Potential Steroid Substitutes. I. Introductory Remarks. The Synthesis of Some Dioxoperhydroanthracenes

BY ROBERT L. CLARKE AND WILLIAM S. JOHNSON

RECEIVED APRIL 10, 1959

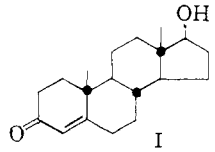
Perhydrogenation of 2,6-anthracenediol followed by oxidation of the crude product gave *cis-syn-cis*-perhydro-2,6-anthracenedione (IVa) and an isomer of IVa which had either the *cis-anti-cis* or *trans-anti-trans* configuration. Reduction of the latter isomer produced a new perhydroanthracene. Addition of two mole-equivalents of 2-ethoxy-1,3-butadiene to benzoquinone produced a mixture of 2,6- and 2,7-diethoxy-1,4,4a,5,8,8a,9a,10a-octahydro-9,10-anthraquinones (XIIIa and XIIIb). Hydrolysis of XIIIa produced perhydro-2,6,9,10-anthracenetetraone (XVa).

Following elucidation of the structure of a number of steroidal hormones and realization of their complexity, considerable effort was devoted to making simple steroid substitutes. It soon became evident that a wide variety of non-steroidal substances could possess estrogenic activity. On the other hand, non-steroidal substitutes for the androgenic and cortical hormones have been conspicuously scarce and of questionable activity.

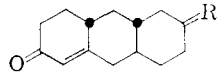
In spite of numerous previous failures, the hope still remains that there may yet be found some simple skeletal structure which, when appropriately substituted by the functional groups known to invest specific activity in the steroid nucleus, will exhibit the corresponding hormonal action. Since androgenic and cortical hormones allow such little latitude in structural variation with retention of activity, it seemed best to test the over-all usefulness of various skeletal structures by making androgenic or cortical hormone analogs. The immediate goal of our work was to prepare a non-steroidal androgen.

As far as we are aware,[1] no non-steroidal compounds have been reported to show consistent androgenic activity with possibly two recent exceptions. A preliminary report by Khaletskii and Zaputryaef[2] declared that 1,2-bis-(1-carbethoxy-2-oxocyclopentyl)-ethane showed androgenic activity in rats, and Farinacci[3] has indicated that 2 - aceto - 13 - methyl - 7 - oxo - 1,2,3,4,5,6,7,9,-10,11,12,13-dodecahydrophenanthrene promotes comb growth in capons.

One of the more obvious approaches to an androgenic substance is to provide a rigid, flat scaffold to hold the functional groups of testosterone (I) in the correct spacial arrangement. Properly substituted hydroanthracenes with their rings



I



IIa, R = H, β OH
IIb, R = H, α OH

fused in a *trans* manner (*cf.* II) seemed to fulfill the requirements, the oxygen functions being only slightly closer together than those in the natural androgens. The immediate objective was to synthesize *dl*-6β- and *dl*-6α-hydroxy-2,3,4,4aβ,5,-6,7,8,8aα,9,10,10aβ - dodecahydro - 2 - anthracenone (IIa and IIb) for testing as androgens. Although IIa resembles testosterone in that the hydroxyl group is β-oriented, this hydroxyl group is, however, axially conformed; hence IIb with an equatorial hydroxyl might serve as a closer model of the hormone. The synthesis of these two compounds was ultimately accomplished[4] and they failed to show hormonal activity. The chemistry involved in the various approaches to these compounds, however, seems worth recording, and is the subject of this and the succeeding two papers.

A direct approach to the synthesis of these hydroanthracenes appeared to be *via* the perhydrogenation of 2,6-anthracenediol, which was readily prepared by stannous chloride reduction of 2,6-dihydroxy-9,10-anthraquinone (anthraflavic acid) to 2,6,9-anthracenetriol[5] followed by aluminum

(1) *Cf.* A. L. Wilds, C. H. Hoffman and T. H. Pearson, THIS JOURNAL, **77**, 647 (1955), and references therein.

(2) A. M. Khaletskii and B. A. Zaputryaef, *J. Gen. Chem.* (*USSR*), **26**, 3026 (1956).

(3) N. T. Farinacci, U. S. Patent 2,830,074, April 8, 1958.

(4) R. L. Clarke and C. M. Martini, THIS JOURNAL, **81**, 5716 (1959). Paper III of this group.

(5) According to the procedure of G. M. Badger and J. W. Cook, *J. Chem. Soc.*, 802 (1939), for the preparation of 1,2-benzanthrol.