It is a characteristic of this reaction that the energy of activation varies greatly with the substituents and that this change is accompanied by a large and parallel change in log PZ. The change in entropy of activation parallels that of log PZ; thus, a large entropy is associated with a large energy of activation and a small entropy with a small energy.

The energies of activation plotted against log PZ (values in Table II) gives a straight line; the relationship is given by the equations

$$\log PZ = 0.60\Delta E^{\ddagger} - 1.4$$

$$\Delta E^{\ddagger} = 1.7 \log PZ + 2.4$$

$$= 0.37\ \Delta S^{\ddagger}_{65.2^{0}} + 23.9$$

The existence of this relationship is evidence that the decomposition reactions of the substituted benzazides proceed through the same mechanism, in spite of the considerable differences in energy and entropy of activation. Although such a functional relationship between energies and entropies of activation, a linear relation, has been observed in various rate processes[25] and has been widely discussed,[25,26] no clear-cut explanation has been given for it. It usually has been explained on the basis of change in solvation,[3,25b,26a] but unfortunately the effect of structural changes on the solvation in the transition state has not yet been investigated in detail. Further investigations, now in progress, on the effect of structural change and solvation may provide a key to this problem.

Acknowledgment.—The authors wish to express their sincere appreciation to Professor M. Murakami and Dr. I. Moritani for their numerous and invaluable suggestions in this work, and also to the Ministry of Education for the partial financial support of this research.

(25) (a) C. N. Hinshelwood, "Kinetics of Chemical Change," The Clarendon Press, Oxford, 1940, pp. 257–261; (b) J. E. Leffler, *J. Org. Chem.*, **20**, 1202 (1955); (c) A. T. Blomquist and J. A. Berstein, THIS JOURNAL, **73**, 5546 (1951); (d) W. K. Wilmarth and N. Schwartz, *ibid.*, **77**, 4543 (1955).

(26) (a) M. G. Evans and M. Polanyi, *Trans. Faraday Soc.*, **32**, 1333 (1936); (b) A. Wassermann, *J. Chem. Soc.*, 621, 623 (1942); (c) R. W. Taft, Jr., THIS JOURNAL, **75**, 4534 (1953); (d) A. Shepp and S. H. Bauer, *ibid.*, **76**, 265 (1954); L. Slutsky and S. H. Bauer, *ibid.*, **76**, 270 (1954).

OSAKA, JAPAN

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, RESEARCH DIVISION, AMERICAN CYANAMID COMPANY, LEDERLE LABORATORIES]

The Synthesis of Certain 5-Deoxy-D-ribofuranosylpurines[1]

BY HENRY M. KISSMAN AND B. R. BAKER

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1,2,3-Tri-*O*-acetyl-5-deoxy-D-ribofuranose (II), obtained in three steps from methyl 2,3-*O*-isopropylidene-5-*O*-mesyl-D-ribofuranoside (IV), was converted to the 1-chloro sugar (I). Condensation of I with chloromercuri-6-dimethylaminopurine, followed by deblocking, afforded 6-dimethylamino-9-(5-deoxy-β-D-ribofuranosyl)-purine (VII). Condensation of I with chloromercuri-6-benzamidopurine afforded, after deblocking, 5′-deoxyadenosine (VIII) mixed with some α-anomer. The use of chloromercuri-6-chloropurine in condensation with I followed by ammonolysis yielded VIII free of anomeric contamination. Ammonolysis of the same condensation product in the cold afforded 6-chloro-9-(5-deoxy-β-D-ribofuranosyl)-purine (XII). Reductive dehalogenation of XII yielded 9-(5-deoxy-β-D-ribofuranosyl)-purine (5′-deoxynebularine, XI).

As part of a general synthetic program in the field of nucleoside analogs,[2] which originated with work on the antibiotic puromycin,[3] it was of interest to determine whether the replacement of the 5′-hydroxyl group of a normal purine riboside with a hydrogen atom would confer any new biological properties to the molecule. The preparation of several 5′-deoxy-D-ribofuranosylpurine nucleosides is the subject of this paper.

The synthesis of these nucleosides was carried out by the method which Davoll and Lowy[4] had developed for the preparation of purine nucleosides and which consisted in the condensation of a purine mercuric chloride derivative with an *O*-acetyl blocked 1-chloro sugar. For the synthesis of the 5′-deoxy-D-ribofuranosyl nucleosides it was necessary to have available 1,2,3-tri-*O*-acetyl-5-deoxy-D-ribofuranose (II) and 5-deoxy-D-ribose (III). After the investigation described in this paper had been completed, Shunk, Lavigne and Folkers[5] reported a synthesis of 5-deoxy-D-ribose (III).[6] Their method for the preparation of III is similar to ours but there are enough experimental differences to warrant a short discussion of our procedure. Methyl 2,3-*O*-isopropylidene-D-ribofuranoside[7] was converted to the crystalline methyl 2,3-*O*-isopropylidene-5-*O*-mesyl-D-ribofuranoside (IV) with methanesulfonyl chloride in pyridine in 63% yield. Transformation of IV to methyl 2,3-*O*-isopropylidene-5-deoxy-5-iodo-D-ribofuranoside (V)[8] was brought about with sodium iodide in refluxing dimethylformamide. Reduc-

(1) Presented in part at the Meeting-in-Miniature, Metropolitan Long Island Subsection, American Chemical Society's New York Section in Brooklyn, New York, on February 15, 1957. Correspondence regarding this communication should be addressed to H. M. K.

(2) For a recent paper in this program, *cf.* H. M. Kissman and M. J. Weiss, *J. Org. Chem.*, **21**, 1053 (1956).

(3) See, for example, paper XI of the puromycin series; H. M. Kissman, C. Pidacks and B. R. Baker, THIS JOURNAL, **77**, 18 (1955).

(4) J. Davoll and B. A. Lowy, *ibid.*, **73**, 1650 (1951).

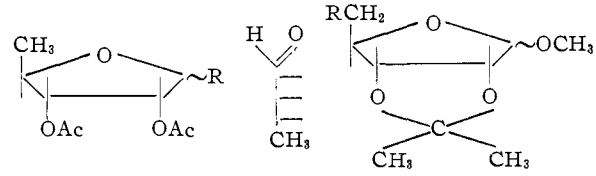
(5) C. H. Shunk, J. E. Lavigne and K. Folkers, *ibid.*, **77**, 2210 (1955).

(6) The phenyl- and *p*-bromophenylosazones of III were obtained from a degradation product of digitoxoseen by F. Micheel, *Ber.*, **63**, 347 (1930).

(7) P. A. Levene and E. T. Stiller, *J. Biol. Chem.*, **104**, 299 (1934).

(8) P. A. Levene and E. T. Stiller, *ibid.*, **106**, 421 (1934), prepared V byr eaction of the less readily obtainable methyl 2,3-*O*-isopropylidene-5-*O*-tosyl-D-ribofuranoside with sodium iodide in acetone in a sealed tube. Shunk, *et al.*,[5] used the Levene and Stiller procedure.

tive dehalogenation of V in methanol, containing triethylamine as an acid acceptor, with either palladium-on-charcoal[5] or Raney nickel afforded methyl 2,3-*O*-isopropylidene-5-deoxy-D-ribofuranoside (VI) as a distillable oil in 70% yield (Raney nickel procedure). Total hydrolysis of VI with dilute hydrochloric acid gave crude 5-deoxy-D-ribose (III) as a sirup which was not purified *per se* but which was characterized as a crystalline 2,4-dinitrophenylhydrazone. Acetylation of crude III with acetic anhydride in pyridine yielded, after distillation, a mixture of acetates, which could be separated into a crystalline solid and a viscous oil. Polarimetric and combustion data indicated that the solid material was 1,2,3-tri-*O*-acetyl-5-deoxy-β-D-ribofuranose (IIa) while the oil was mainly the corresponding α-anomer (IIb) contaminated with some β-anomer and a small amount of a methyl glycoside (probably methyl 2,3-di-*O*-acetyl-5-deoxy-D-ribofuranoside). The conversion of either anomer of II or of the distilled anomeric mixture to a crude, sirupy 1-chloro sugar (I) was carried out in the usual manner with ethereal hydrogen chloride.



I, R = Cl
IIa, R = OAc; β-anomer
IIb, R = OAc; α-anomer

III

IV, R = OMs
V, R = I
VI, R = H

The first nucleoside to be prepared in this investigation was **6-dimethylamino-9-(5-deoxy-β-D-ribofuranosyl)-purine (VII)**. This substance was of interest as an analog of 6-dimethylamino-9-(3-amino-3-deoxy-β-D-ribofuranosyl)-purine, the aminonucleoside obtained from the antibiotic puromycin.[9] Compound VII was synthesized by condensation of chloromercuri-6-dimethylaminopurine[10] with the freshly prepared 1-chloro sugar (I). The crude condensation product was de-*O*-acetylated with methanolic sodium methoxide to afford VII as a crystalline solid in 27% yield [over-all from the sugar triacetate (II)]. Proof that the sugar had entered the 9-position of the purine ring was adduced from the compound's ultraviolet absorption maximum at 274 mμ.[11] While the assignment of the β-configuration to VII is not unequivocal, such a configuration is likely in view of the relatively high negative rotation [$[\alpha]_D$ −50.7° (ethanol)] of the compound[12] and the method by which it was prepared.[13,14]

The synthesis of **5′-deoxyadenosine** [(6-amino-9-(5-deoxy-β-D-ribofuranosyl)-purine (VIII)] proved to be somewhat more complicated. Initial attempts *via* the condensation of chloromercuri-6-benzamidopurine[4] with the halo sugar (I) resulted in the formation of anomeric mixtures of nucleosides. Although these mixtures contained only small amounts of the α-anomer, their resolution was difficult. The condensation reaction was carried out in the usual manner in refluxing xylene and the resulting crude condensation product was deblocked by heating with methanolic sodium methoxide. When the heating period was 30 minutes, there was obtained, after partition chromatography, a fraction which still retained the N-benzoyl grouping as evidenced by its infrared and ultraviolet absorption spectra. Additionally, there was isolated the desired β-nucleoside VIII in 11% yield over-all from the triacetate II. Compound VIII had the characteristics expected for an adenosine analog.[15] The corresponding deblocked α-anomer was not observed in this experiment. When the period for the methoxide-catalyzed deblocking reaction was extended to 75 minutes, hydrolysis of the N-benzoyl group was complete and there was isolated crystalline VIII in 19% yield and also another crystalline product which was largely the corresponding α-nucleoside (IX) (3% yield). It would appear that the N-benzoyl compound observed after the 30 minute heating period was a derivative of the α-anomer and that this was less readily hydrolyzed than the corresponding derivative of the β-anomer.

The problem of isolating 5′-deoxyadenosine from the anomeric mixtures obtained in the synthesis just described made another approach desirable. Inasmuch as the use of chloromercuri-6-benzamidopurine had led to the formation of an α-nucleoside in another case[16] it seemed advisable to investigate the applicability of another purine mercuric chloride derivative, namely, chloromercuri-6-chloropurine. Brown and Weliky[17] had successfully condensed tri-*O*- acetyl-D-ribofuranosyl chloride with the mercuric chloride derivative of 6-chloropurine[18] to give the blocked 6-chloro nucleoside which was converted to adenosine by treatment with ammonia. In an analogous manner, we were able to condense chloromercuri-6-chloropurine with the chloro sugar (I) to obtain 6-chloro-9-(2,3 - di - *O* - acetyl - 5 - deoxy - D - ribofuranosyl)-purine (X) as a gum. Treatment of X with meth-

(9) B. R. Baker, J. P. Joseph and J. H. Williams, THIS JOURNAL, **77**, 1 (1955).

(10) B. R. Baker, J. P. Joseph and J. H. Williams, *J. Org. Chem.*, **19**, 1780 (1954).

(11) Condensations of chloromercuri-6-dimethylaminopurine with certain 1-chloro sugar derivatives have also yielded 6-dimethylamino-7-glycosylpurines; *cf.* B. R. Baker, J. P. Joseph and R. E. Schaub, THIS JOURNAL, **77**, 5905 (1955). However, these 7-substituted 6-dimethylaminopurines have λ_{max} 297 mμ.[10]

(12) The rotation of the corresponding 6-dimethylamino-9-β-D-ribofuranosylpurine is $[\alpha]_D$ −62.6° (water).[3]

(13) B. R. Baker, J. P. Joseph, R. E. Schaub and J. H. Williams, *J. Org. Chem.*, **19**, 1786 (1954) have postulated the rule "that when a halo acetylated sugar is coupled with a heavy metal salt of a purine, the resulting nucleoside will have the C_1–C_2 *trans* configuration," [14] (C_1–C_2 *trans* rule).

(14) B. R. Baker, R. E. Schaub and H. M. Kissman, THIS JOURNAL, **77**, 5911 (1955).

(15) It had an ultraviolet maximum at λ_{max}^{EtOH} 259 mμ (ε 13,760) and a rotation of $[\alpha]_D$ −54° (ethanol). Adenosine has $\lambda_{max}^{H_2O}$ 259 mμ (ε 15,400) and $[\alpha]_D$ −61.7° (water).

(16) The formation of an α-ribosylpurine derivative in the condensation of chloromercuri-6-benzamidopurine with 1-*O*-acetyl-2,5-di-*O*-benzoyl-3-acetamido-3-deoxy-D-ribofuranose in the presence of titanium tetrachloride has been observed by Baker, Schaub and Kissman.[14] At that time, this apparent exception to the "C_1–C_2 *trans* rule"[13] was attributed to the presence of the titanium tetrachloride; *cf.* L. Goldman, J. W. Marsico and R. B. Angier, THIS JOURNAL, **78**, 4173 (1956).

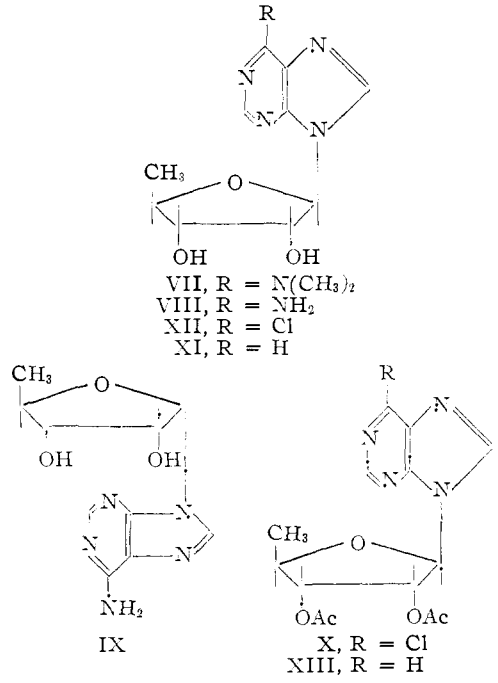
(17) G. B. Brown and V. S. Weliky, *J. Biol. Chem.*, **204**, 1019 (1953).

(18) A. Bendich, P. J. Russell, Jr., and J. J. Fox, THIS JOURNAL, **76**, 6073 (1954).

anolic ammonia in a sealed tube gave crystalline 5′-deoxyadenosine (VIII) which was identical in all respects with the β-anomer obtained in the first synthesis. The compound was obtained in 21% yield over-all from the triacetate II. There was no evidence for the formation of an α-anomer in this preparation and this seemed to support the hypothesis that the use of chloromercuri-6-benzamidopurine in the first synthesis had led to the formation of the α-anomer. However, since the completion of this work, the chloro sugar (I) has been condensed with 5,6-dichlorobenzimidazole mercuric chloride derivative[19] and in this instance, too, there was obtained a small amount of an α-anomer [1-(5-deoxy-α-D-ribofuranosyl)-5,6-dichlorobenzimidazole] as a by-product. It now appears that these exceptions to the "C_1-C_2 *trans* rule"[13] are connected not only with the nature of the purine mercuric chloride derivative used in the condensation reaction and with the conditions of that reaction but also with the structure of the sugar derivative. Furthermore, it would appear that 1-chloro-2,3-di-O-acetyl-5-deoxy-D-ribofuranose (I) affords these α-anomeric by-products rather readily. With respect to the validity of the "C_1–C_2 *trans* rule," it should be emphasized that experience to date indicates that anomers having the C_1–C_2 *cis* configuration are not often observed; and when they are observed, they are present in only minor quantity.

The blocked 6-chloronucleoside (X), obtained above, was also used for the synthesis of **5′-deoxynebularine** [9-(5-deoxy-β-D-ribofuranosyl)-purine] (XI) an analog of nebularine, which is a toxic principle isolated from the mushroom *Agaricus Nebularis* Batsch.[20] The synthesis of XI followed the method used by Brown and Weliky[17] for the preparation of nebularine itself. Removal of the *O*-acetyl groups from X was effected with cold methanolic ammonia and there was obtained crystalline 6-chloro-9-(5-deoxy-D-ribofuranosyl)-purine (XII) in 18% yield over-all from II. Reductive dehalogenation of XII with hydrogen at atmospheric pressure in the presence of palladium on charcoal catalyst and magnesium oxide as acid acceptor[17] afforded 5′-deoxynebularine (XI) as a crystalline solid (29% yield), whose ultraviolet absorption spectrum with its maximum at 264 mμ agreed well with that reported for nebularine.[17] The synthesis of XI could be varied by first reducing the blocked compound X under the conditions described above. This yielded crystalline 9-(2,3-di-*O*-acetyl-5-deoxy-β-D-ribofuranosyl)-purine (XIII), which on de-*O*-acetylation with methanolic sodium methoxide afforded XI (25% yield) identical with the material obtained by the former route. Since the blocked 6-chloro nucleoside X has also been converted to 6-amino-9-(5-deoxy-D-ribofuranosyl)-purine (VIII), the β-configuration of which is certain by virtue of the fact that the α-anomer has also been isolated, it follows that XI must also have the β-configuration.

The nucleosides described in this paper are inactive against the transplanted adenocarcinoma of the C3H mouse.[21]



Acknowledgment.—We are grateful to Dr. M. J. Weiss for discussions helpful in the preparation of this paper and to Mr. C. Pidacks for advice on partition chromatography. Microanalyses were carried out by Mr. L. Brancone and staff and spectroscopic and polarimetric work by Mr. W. Fulmor and staff.

Experimental[22]

Methyl 2,3-*O*-Isopropylidene-5-*O*-mesyl-D-ribofuranoside (IV).—To an ice-cold solution of 30.6 g. (0.15 mole) of distilled methyl 2,3-*O*-isopropylidene-D-ribofuranoside[7] in 90 cc. of reagent pyridine was added, dropwise with good mixing and cooling, 17.4 cc. of methanesulfonyl chloride. The mixture was kept at 5° overnight and was then added to 400 cc. of ice-water. This resulted in the precipitation of a crystalline solid. The mixture was extracted with three 100-cc. portions of chloroform and the combined extracts were washed twice with 25-cc. portions of water and were then dried and partially decolorized over magnesium sulfate and decolorizing carbon (Norite). The filtered solution was evaporated *in vacuo* and the residue was dissolved in 500 cc. of ether and the solution was filtered through Norite. The light yellow filtrate was concentrated to a volume of 40 cc. and the crystalline solid which separated was collected and washed with a little ether. Further concentration of the mother liquors afforded additional crops of solid. Thus, there was obtained 26.8 g. (63%) of material with m.p. 74–76°. For analysis, material obtained in a similar preparation was recrystallized from ethyl acetate–cyclohexane; m.p. 78–79°. $[\alpha]^{24}D$ −53.0° (*c* 1.86 in chloroform).

Anal. Calcd. for $C_{10}H_{18}SO_7$: C, 42.52; H, 6.42. Found: C, 42.71; H, 6.39.

Methyl 2,3-*O*-Isopropylidene-5-deoxy-5-iodo-D-ribofuranoside (V).[8]—A stirred solution of the mesyl derivative IV (8.5 g., 0.03 mole) in 90 cc. of dimethylformamide was refluxed with 5.06 g. (0.033 mole) of dry sodium iodide for 30 minutes. The mixture was then cooled and filtered from inorganic precipitate. The latter was washed with

(19) H. M. Kissman, R. G. Child and M. J. Weiss, THIS JOURNAL, **79**, 1185 (1957).

(20) N. Löfgren and B. Lüning, *Acta Chem. Scand.*, **7**, 225 (1953); N. Löfgren, B. Lüning and H. Hedström, *ibid.*, **8**, 670 (1954).

(21) Private communication from Dr. J. J. Oleson of these laboratories.

(22) Melting points were taken on a Kofler micro hotstage and are corrected. Ultraviolet absorption spectra were determined on a Cary recording spectrophotometer and infrared spectra on a Perkin–Elmer double beam spectrophotometer, model 21.

ether and the combined filtrates were evaporated under reduced pressure in a 70° bath to a volume of about 30 cc. To this solution was added 300 cc. of water and the mixture was extracted with seven 50-cc. portions of ether. The combined extracts were dried over magnesium sulfate, clarified with Norite, filtered and evaporated under reduced pressure (water pump) in an 80–90° bath. This left 8.4 g. (89%) of light yellow oil[23] which was distilled at 101–109° (0.2 mm.) to afford 7.2 g. (76%) of colorless liquid. Material obtained in a similar experiment was used for analysis; b.p. 75–80° (0.1 mm.); $\alpha^{24.5}D$ −68.6° (*c* 2 in chloroform).

Anal. Calcd. for $C_9H_{15}O_4I$: C, 34.41; H, 4.81; I, 40.41. Found: C, 36.37; H, 5.16; I, 39.44.[24]

Methyl 2,3-*O*-Isopropylidene-5-deoxy-D-ribofuranoside (VI).[5] (a) **With Palladium-on-charcoal Catalyst.**—To a solution of 3.22 g. (10.2 mmoles) of the 5-iodo derivative V in 30 cc. of methanol containing 1.56 cc. of triethylamine was added a small piece of Dry Ice and then 0.322 g. of 10% palladium-on-charcoal catalyst. The stirred mixture was hydrogenated under atmospheric pressure until the uptake of hydrogen had ceased. The solution was filtered through a bed of Celite[25] and the filtrate was evaporated under reduced pressure in a 30° bath to a small volume. The residual solution was mixed with 50 cc. of methylene chloride and the mixture was extracted with 10 cc. of water and 10 cc. of a saturated aqueous sodium bicarbonate solution. The methylene chloride solution was dried over magnesium sulfate, filtered and evaporated *in vacuo* (water pump) in a 30° bath. The residue was distilled through a small Vigreux column and there was obtained 1.08 g. (56%); b.p. 92–95° (20 mm.).

Anal. Calcd. for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.41; H, 8.76.

(b) **With Raney Nickel Catalyst.**[26]—To a solution of 32.5 g. (0.103 mole) of the undistilled[23] iodo derivative V in 100 cc. of reagent methanol containing 30 cc. of triethylamine was added 3 g. of Raney nickel catalyst[26] in 20 cc. of methanol. The mixture was shaken at room temperature in a Parr hydrogenation apparatus at 35 lb. starting pressure until the calculated amount of hydrogen had been taken up (19 minutes). The mixture was filtered and the catalyst was washed with methanol. The filtrate was freed from solvent under reduced pressure at room temperature and the residue was triturated with ether and the solution was filtered from crystalline triethylamine hydroiodide (calcd. 23.7 g., found 19.9 g.). The filtrate (200 cc.) was washed with 10-cc. portions of water, saturated sodium bicarbonate solution and water. It was then dried over magnesium sulfate, filtered and freed from solvent by evaporation on the steam-bath. The residue was distilled and there was obtained 13.96 g. (71%); b.p. 95–99° (20–25 mm.).

5-Deoxy-D-ribose (III).—A mixture of 825 mg. (4.4 mmoles) of methyl 2,3-*O*-isopropylidene-5-deoxy-D-ribofuranoside (VI) and 12 cc. of 0.04 *N* hydrochloric acid was heated for two hours on the steam-bath with occasional shaking. The resulting solution was brought to room temperature and was diluted with 40 cc. of water, neutralized by the addition of Duolite A-4 anion-exchange resin (OH form)[27] and filtered. The resin was washed with a little water and filtrate and washings were combined and evaporated *in vacuo* in a 50° bath. The residue was further dried by a double evaporation with benzene and by storage over phosphorus pentoxide *in vacuo*. There was obtained 575 mg. (97%) of a light yellow sirup which gave a strong positive Benedict test on warming. The sugar was not further purified but was used as such in the acetylation step (see below).

For characterization, 269 mg. (2 mmoles) of crude III was converted to the **2,4-dinitrophenylhydrazone** by the method of Lloyd and Doherty.[28] The sugar, dissolved in 0.5 cc. of water, was added to a suspension of 396 mg. (2 mmoles) of 2,4-dinitrophenylhydrazine in 12 cc. of absolute ethanol. The mixture was heated under reflux for 12 hours during which time the hydrazine reagent had gone into solution. It was then evaporated to dryness under reduced pressure and the residue was crystallized from ethyl acetate–ether to afford in several fractions, 453 mg. (72%) of yellow solid; m.p. 142–145°. Several recrystallizations from benzene–methylene chloride (with Norite) raised the m.p. to 151–152° dec.; $[\alpha]^{25}D$ −30.2° (*c* 0.99 in methanol).

Anal. Calcd. for $C_{11}H_{14}O_4N_4$: C, 42.04; H, 4.49; N, 17.83. Found: C, 42.47; H, 4.43; N, 18.14.

1,2,3-Tri-*O*-acetyl-5-deoxy-D-ribose (II).—To a solution of 575 mg. (4.4 mmoles) of crude sugar III in 20 cc. of reagent pyridine was added 3 cc. of acetic anhydride. The mixture was allowed to stand at room temperature for 3 days and was then mixed with 50 cc. of ice cold saturated aqueous sodium bicarbonate solution. The reaction mixture was extracted with five 10-cc. portions of chloroform and the extracts were dried over magnesium sulfate, filtered and evaporated under reduced pressure. Remaining traces of pyridine were removed by repeated evaporations with toluene. The residue was taken up in anhydrous ether and was clarified by filtration through Darco (decolorizing carbon). Evaporation of this solution left 960 mg. of residue which was distilled *in vacuo* at 115–120° (0.2 mm.) to afford 746 mg. (64.5%) of a colorless oil which solidified partially on standing. A middle fraction (b.p. 118–120° (0.2 mm.)) was used for analysis.

Anal. Calcd. for $C_{11}H_{16}O_7$: C, 50.77; H, 6.20; OAc, 49.5; OMe, 0.0. Found: C, 50.63; H, 6.41; OAc, 49.0; OMe, 1.4.

In another experiment, 1.88 g. (10 mmoles) of the methyl glycoside VI was hydrolyzed and acetylated as described above. From evaporation of the colorless ether solution, there was obtained 2.49 g. (96% over-all from VI) of oily mixed acetates. This was not distilled but was partially crystallized from hexane. The solid was collected and recrystallized from hexane to afford 766 mg. (29%) of β-anomer (**IIa**); m.p. 61–64°. Additional recrystallizations from hexane–ether gave 545 mg. of well-formed crystals, m.p. 64–65°; $[\alpha]^{25}D$ −26.9° (*c* 2.42 in chloroform). For analysis, a sample was sublimed *in vacuo* without change in m.p.

Anal. Calcd. for $C_{11}H_{16}O_7$: C, 50.77; H, 6.20. Found: C, 50.63; H, 6.41.

Distillation of the mother liquors from which this solid had been obtained afforded 829 mg. (32%) of oil (b.p. 100–103° (0.1 mm.)); $[\alpha]^{25}D$ +17.0° (*c* 2.71 in chloroform). This oil was considered to be mainly the α-anomer IIb, contaminated with some β-anomer and with a small amount of a methyl glycoside.

Anal. Calcd. for $C_{11}H_{16}O_7$: C, 50.77; H, 6.20; OMe, 0.0. Found: C, 50.29; H, 6.39; OMe, 1.7.

6-Dimethylamino-9-(5-deoxy-β-D-ribofuranosyl)-purine (VII).—The distilled[29] mixture of triacetates (IIa and IIb) (2.6 g., 10 mmoles) was dissolved in 80 cc. of anhydrous ethereal hydrogen chloride (saturated at 0°) and the solution was allowed to stand in a flask protected from moisture at −3° for 72 hours. It was then evaporated under reduced pressure and last traces of hydrogen chloride were removed from the residue by distillation *in vacuo* with anhydrous benzene. The gummy **chloro sugar (I)** was taken up in 25 cc. of anhydrous xylene and the solution was added to an azeotropically dried suspension of chloromercuri-6-dimethylaminopurine on Celite[10,25] (6.25 g. of the mixture containing 3.88 g., 10 mmoles, of the purine derivative) in 100 cc. of xylene. The stirred mixture was allowed to reflux for three hours and was then filtered. The precipitate was washed with chloroform and the combined filtrates were evaporated under reduced pressure. The residue was dissolved in 80 cc. of chloroform and the solution was freed from a small amount of insoluble material by filtration. The filtrate was washed with 20 cc. of a 30% aqueous potassium iodide solution and then with 20 cc. of water. The

(23) Materiaf of this quality was pure enough for subsequent reactions.

(24) This analysis has been repeated several times with equally unsatisfactory results on material obtained from different preparations. Levene and Stiller[8] report only iodine and methoxyl analyses.

(25) Cefite is a product of the Johns-Manville Corporation.

(26) R. Mozingo, D. E. Wolf, S. A. Harris and K. Folkers, THIS JOURNAL, **65**, 1013 (1943).

(27) Duolite A-4 is a product of the Chemical Process Company, Redwood City, California.

(28) E. A. Lloyd and D. G. Doherty, THIS JOURNAL, **74**, 4214 (1952).

(29) Similar results were obtained when either the crystalline anomer IIa or the distilled oil containing mostly the α-anomer IIb was used.

organic phase was dried over magnesium sulfate, clarified with Darco, filtered and evaporated under reduced pressure. There was obtained 3.14 g. of a dark yellow gum which contained a maximum of 72% of 6-dimethylamino-9-(2,3-di-*O*-acetyl-5-deoxy-D-ribofuranosyl)-purine as determined by ultraviolet absorption analysis.[30] The material was not further purified, but was dissolved in 50 cc. of absolute methanol and to the solution was added 0.3 cc. of *N* methanolic sodium methoxide solution. The mixture was refluxed for 30 minutes during which time it remained alkaline. Evaporation of the solvent *in vacuo* left 2.09 g. of a dark residue which was partially decolorized by solution in absolute acetone and filtration through a layer of Darco. The filtrate was again evaporated *in vacuo* and the residue was crystallized from isopropyl alcohol to yield 771 mg. (27%), m.p. 160–165°, of a fluffy white solid. For analysis, a portion of this material was recrystallized once more from isopropyl alcohol; m.p. 163–165°; $[\alpha]^{24.5}D$ −50.7° (*c* 2.02 in ethanol). In the ultraviolet, the compound showed the expected[3] maxima at 268 mμ (ε 18,620 in acid), 274 mμ (ε 18,400 in ethanol), and 274 mμ (ε 18,620 in base).[31]

Anal. Calcd. for $C_{12}H_{17}O_3N_5$: C, 51.60; H, 6.14; N, 25.08. Found: C, 51.82; H, 6.24; N, 25.38.

6-Chloro-9-(2,3-di-*O*-acetyl-5-deoxy-β-D-ribofuranosyl)-purine (X).—A solution of the chloro sugar (I), prepared as above from 1.3 g. (5 mmoles) of II in 10 cc. of xylene was added to an azeotropically dried suspension of chloromercuri-6-chloropurine on Celite[32] (4 g. of the mixture containing 2 g., 5 mmoles, of the purine derivative) in 140 cc. of xylene. The stirred mixture was allowed to reflux for three hours and was then worked up as described for the preceding reaction. The dark reaction product was partially decolorized by treatment with Darco in ether solution. The filtered solution was freed from solvent under reduced pressure to afford 1.63 g. of a yellow gum which contained a maximum of 74% of X as determined by ultraviolet absorption analysis at 264 mμ (the extinction of 6-chloro-9-β-D-ribofuranosylpurine[17] at this absorption maximum was used for comparison). This represents a maximum yield of 68% over-all from II.

6-Chloro-9-(5-deoxy-β-D-ribofuranosyl)-purine (XII).—The crude blocked 6-chloronucleoside (X) obtained above (1.6 g.) was mixed with 25 cc. of methanolic ammonia (saturated at 3°) and the solution was allowed to remain at −3° for 16 hours. It was then freed from ammonia and methanol under reduced pressure at 25° to afford 1.38 g. of residue. A small amount of this material was taken up in hot ethyl acetate, filtered from traces of insoluble material and diluted with ether to give an amorphous solid. This material was partially contaminated with an adenosine derivative (probably VIII) as shown by its absorption maximum at 260 mμ (instead of 264 mμ) in the ultraviolet and at 5.97 μ (indicative of a 6-aminopurine derivative) in the infrared. The bulk of the reaction product was dissolved in hot ethyl acetate, filtered through a layer of Darco and evaporated to dryness. There was obtained 1.03 g. of gum mixed with a small amount of crystalline material (m.p. 151–154°). The gum was dissolved in a minimum of ethyl acetate and the solution was seeded with the solid material and was then diluted with benzene till cloudy. The solid material which crystallized on standing was collected, washed with ether and dried to afford 301 mg., m.p. 141–144°. Another 54 mg. with the same m.p. was obtained by concentration of the mother liquor. The substance was recrystallized twice from small amounts of ethyl acetate; 247 mg. (18% yield over-all from II), m.p. 154–156°. For analysis, the substance was crystallized twice more from ethyl acetate and once from methylene chloride–ether without change in m.p. The compound had $[\alpha]^{24}D$ −45.5° (*c* 1.69 in ethanol) and $\lambda_{max}^{ethanol}$ 264 mμ (ε 9,100 in acid; ε 8,750 in ethanol; ε 9,000 in base).[31]

Anal. Calcd. for $C_{10}H_{11}O_3NCl$: C, 44.38; H, 4.10; N, 20.70; Cl, 13.10. Found: C, 44.65; H, 4.17; N, 20.68; Cl, 12.84.

6-Amino-9-(5-deoxy-β-D-ribofuranosyl)-purine (5′-Deoxyadenosine) (VIII). From 6-Benzamidopurine (A).—A solution of the chloro sugar (I), prepared from 2.60 g. (10 mmoles) of IIa as above, was added to an azeotropically dried suspension of chloromercuri-6-benzamidopurine[4] on Celite (10.2 g. of the mixture containing 4.74 g., 10 mmoles, of the purine derivative) in 120 cc. of xylene. The stirred reaction mixture was allowed to reflux for 3 hours and was then worked up as described for the synthesis of VII. There was obtained 3.68 g. of reaction product as a dark yellow gum. For removal of the acyl groups, the material was dissolved in 50 cc. of absolute methanol and to the solution was added 1 cc. of *N* methanolic sodium methoxide solution. The mixture was heated under reflux for 30 minutes and then evaporated *in vacuo*. There was obtained 1.92 g. of a residual dark gum which still was contaminated with methyl benzoate.

For **partition chromatography**, 1.2 g. of this material was dissolved in 60 cc. of water, filtered and treated with a small amount of Amberlite IRC-50 cation exchange resin (H form)[33] until the solution was neutral. The yellow filtrate was treated with Darco, refiltered and evaporated under reduced pressure. The residue (770 mg.) was dissolved in 5 cc. of water, which had been saturated with ethyl acetate, and the solution was mixed with 10 g. of Celite.[34] This mixture was packed on top of a column which had been prepared[3] from 230 g. of Celite and 115 cc. of water saturated with ethyl acetate. The column (54 cm. × 3.8 cm.) whose hold back volume (h.b.v.)[35] was 320 cc., was developed with ethyl acetate which had been saturated with water and the effluent was allowed to run through a Beckman DU spectrophotometer (set at 260 mμ) which was connected to a Brown strip-chart recorder (0–50 mv.). Material having absorption in the 260 mμ region was eluted in the 1st h.b.v. Evaporation of an aliquot afforded a gum which in the ultraviolet had $\lambda_{max}^{ethanol}$ 280 mμ. In the infrared the substance showed λ_{max}^{KBr} 5.84 μ but no absorption at 5.67 or 6.05 μ. This seemed to indicate that the material still contained the 6-benzamido group but that the *O*-acetyl groups had been removed. The contents of this 1st h.b.v. were not further investigated. Continued development of the column yielded in the 3rd and 4th h.b.v. additional material with absorption in the 260 mμ region. These fractions were pooled and evaporated under reduced pressure and the residue was crystallized to afford 183 mg. (11% yield over-all from IIa) of solid, m.p. 169–174°. For analysis, the compound was recrystallized thrice from ethanol and there was obtained, after drying *in vacuo* at 110° for two hours, 60 mg., m.p. 210–212° (liquefied at 180° and resolidified). The compound had a specific rotation of $[\alpha]^{25}D$ −52.7° (*c* 1.00 in ethanol) and showed the following maxima in the ultraviolet: $\lambda_{max}^{ethanol}$ 257 mμ (ε 14,280 in acid), 259 mμ (ε 13,760 in ethanol), 259 mμ (ε 14,280 in base).[31]

Anal. Calcd. for $C_{10}H_{13}O_3N_5$: C, 47.80; H, 5.22; N, 27.88. Found: C, 47.98; H, 5.53; N, 27.33.

(B).—In another experiment, the crude condensation product (3.76 g.), obtained as described above from 10 mmoles of the sugar triacetate II, was deblocked by refluxing for 75 minutes in 50 cc. of methanol containing 1 cc. of *N* methanolic sodium methoxide solution. The mixture remained basic throughout the reaction period. After removal of the solvent *in vacuo*, the residue was dissolved in 50% aqueous ethanol and the brown solution was stirred with Amberlite IRC-50 cation-exchange resin[33] until neutral. The mixture was filtered and evaporated *in vacuo*. The residue was redissolved in 50 cc. of water and the solution was extracted several times with small amounts of ethyl acetate to remove last traces of methyl benzoate. The aqueous solution was evaporated *in vacuo* and the residue was dried to afford 1.49 g. of glass. This was dissolved in

(30) The absorption of 6-dimethylamino-9-β-D-ribofuranosylpurine[3] at 274 mμ was used for comparison.

(31) The compound was dissolved in ethanol. Aliquots were diluted 1:10 with 0.1 *N* hydrochloric acid for the acid spectrum and 1:10 with 0.1 *N* sodium hydroxide for the base spectrum.

(32) The chloromercuri derivative was prepared according to Brown and Weliky[17] with the addition of Celite[25] as described previously.[1] More uniform batches of this material have been obtained since then by the addition of sodium hydroxide to molar equivalents of mercuric chloride and 6-chloropurine in aqueous alcohol. The 6-chloropurine was obtained from the Francis Earle Laboratories, Inc., Peekskill, New York.

(33) This resin is a product of the Rohm and Haas Company, Philadelphia, Pa.

(34) The material used in these partition columns was Celite 545[25] which had been washed with 6 *N* hydrochloric acid and then with distilled water until neutral and finally with methanol. The substance was dried at 50°.

(35) Hold back volume is defined as the volume of solvent necessary to fill the column.

absolute ethanol, filtered through a layer of Darco and concentrated to a volume of 15 cc. The solution was seeded with crystals of VIII, obtained in the previous experiment, and the crystalline solid which formed was collected and washed with a little ethanol and with ether. Drying *in vacuo* afforded solid with m.p. 165–180° (shrinking at 120°); after two recrystallizations from ethanol there was obtained 472 mg. (19% yield over-all from II); m.p. 205–207° (shrinking at 120 and 185°). This was undepressed by admixture of the material obtained in experiment A. The mother liquors were pooled and evaporated and there was obtained 720 mg. of glass which contained a maximum of 63% of an adenosine derivative, as determined by ultraviolet absorption analysis, and whose infrared spectrum was practically identical to that of the crystalline material obtained in experiment A. The glass was dissolved in hot ethyl acetate–ethanol and the solution was concentrated at the b.p. Successive fractions of gum precipitated on cooling and were removed, combined and redissolved in a minimum amount of ethanol. A white precipitate formed after long standing in an ice-bath. It was collected, washed with a little ethanol and with ether. The dried material weighed 123 mg. (3% yield over-all from II); m.p. 174–179° (shrinking at 120°). Recrystallization from ethanol afforded 57 mg., m.p. 173–175° (shrinking at 115–120°). The ultraviolet and infrared absorption spectra of this substance were identical to those of the compound obtained in experiment A. The specific rotation was $[\alpha]^{24.5}D$ −9.9° (*c* 1.62 in ethanol) and the substance was considered to be largely the **α-anomer (IX)** of 5′-deoxyadenosine.

Anal. Calcd. for $C_{10}H_{13}O_3N$: C, 47.80; H, 5.22; N, 27.88. Found: C, 47.20; H, 5.57; N, 27.34.

(C).—Another experiment was carried out under the same conditions and with the same amount of reagents as described under (B). There was obtained 1.3 g. of deblocked material which, according to ultraviolet absorption analysis, contained a maximum of 71% of an adenosine derivative. The material was partitioned in an ethyl acetate–water system on 210 g. of Celite[34] as described under (A). Very little material with absorption at 260 mμ was eluted in the 1st and 2nd h.b.v.[36] The 4th h.b.v. afforded 279 mg. of a crude solid which was recrystallized from ethanol to give 197 mg., m.p. 206–208° (with partial melting and resolidification at 125–130°); $[\alpha]^{24}D$ −36.9° (*c* 1.5 in ethanol). This substance was mostly the β-anomer and the 197 mg. represents an 8% over-all yield from II (10 mmoles). Continued development of the column afforded 302 mg. of crude solid in the 5th and the first half of the 6th h.b.v. Recrystallization from ethanol gave 173 mg. of solid which melted unsharply at 115° but did not resolidify. This portion (6.9% over-all yield from II) was considered to be an anomeric mixture. In the second half of the 6th h.b.v. there was obtained 67 mg. of crude and 46 mg. of recrystallized solid with m.p. 110–115° and $[\alpha]^{24}D$ +53.0° (*c* 0.75 in ethanol). Further attempts to isolate the pure anomers by partition chromatography were only partially successful.[37] In view of the fact that a better synthesis for the preparation of VIII was found (see below) these experiments were discontinued.

From the Blocked 6-Chloronucleoside (X).—The tri-*O*-acetyl sugar (II) (0.65 g., 2.5 mmoles) was converted to the 6-chloronucleoside (X) as described above and there was obtained 777 mg. of a crude gum which contained a maximum of 67% of X by ultraviolet absorption analysis. The gum was dissolved in 25 cc. of methanolic ammonia (saturated at 0°) and the solution was heated in a sealed tube for 5 hours on the steam-bath. The tube was then cooled in an ice-bath and its contents were evaporated under reduced pressure. The residue was dissolved in a small amount of hot ethanol and the brown solution was partially decolorized with Darco. The filtered solution was allowed to cool and the solid, which crystallized, was collected, washed with a little ethanol and dried; 141 mg., m.p. above 125° but undefined; $[\alpha]^{24}D$ −48.2° (*c* 1.02 in ethanol); 91% purity by ultraviolet absorption analysis. The mother liquors were evaporated and the residue was dissolved in water to give a dark solution which could be decolorized with a little Darco. The filtrate was once more evaporated *in vacuo*, the residue was dissolved in a minimum amount of ethanol and the solution was diluted with ethyl acetate till cloudy. The solid which precipitated from this mixture was inorganic and was discarded. The filtrate was once more evaporated and the residue was dissolved in a minimum amount of hot water and was allowed to stand in an open vessel. After several days there was obtained 33 mg. of solid with undefined m.p. Its purity was 88% (ultraviolet absorption analysis and it had $[\alpha]^{24}D$ −49.7° (*c* 0.19 in ethanol). The combined solids (33 mg. and 141 mg.) were recrystallized from ethanol to give 136 mg. (21% yield over-all from II), m.p. 208–209°. Analytical samples were obtained by recrystallization from water (m.p. 203–205°) or from ethanol (m.p. 200–203°). Samples were dried at 110° for 3 hours *in vacuo*; $[\alpha]^{24}D$ −54.0° (*c* 0.63 in ethanol). The ultraviolet and infrared spectra were identical with those obtained from samples of VIII which had been prepared in experiments A or B.

Anal. Calcd. for $C_{10}H_{13}O_3N_5$: C, 47.80; H, 5.22; N, 27.88. Found: (from water) C, 47.74; H, 5.16; N, 27.51; (from ethanol) C, 48.16; H, 5.36; N, 27.74.

9-(2,3-Di-*O*-acetyl-5-deoxy-β-D-ribofuranosyl)-purine (XIII).—The blocked 6-chloronucleoside (X) was prepared from 1.40 g. (5.38 mmoles) of II as described above and there was obtained 1.67 g. of a gum which contained a maximum of 80% (*i.e.*, 3.75 mmoles) of X as determined by ultraviolet absorption analysis. The gum was dissolved in 50 cc. of ethanol and there was added 367 mg. of 10% palladium-on-charcoal catalyst, which had been wetted with 2 cc. of methyl cellosolve, and 151 mg. of magnesium oxide.[17] The stirred suspension was hydrogenated under atmospheric pressure until the calculated amount of hydrogen had been taken up (3 hours). The reaction was stopped and the mixture was filtered through Celite. The catalyst on the filter was washed with ethanol and the combined filtrates were evaporated *in vacuo*. The residue was dissolved in 50 cc. of chloroform and the solution was washed with two 10-cc. portions of water. The chloroform solution was dried over magnesium sulfate, filtered and freed from solvent *in vacuo*. The residue (1.33 g.) was dissolved in 20 cc. of ether and the solution was mixed with hexane at the b.p. until cloudy. The granular precipitate which formed was collected and dried to yield 404 mg., m.p. 104–106°. This was recrystallized several times from ether–methylene chloride; 339 mg. (19% yield over-all from II), m.p. 119–120°; $[\alpha]^{24}D$ −26.8° (*c* 1.49 in ethanol); $\lambda_{max}^{ethanol}$ 261 mμ (ε 5720 in acid); 262 mμ (ε 7050 in ethanol), 262 mμ (ε 7170 in base).[31]

Anal. Calcd. for $C_{14}H_{16}O_5N_4$: C, 52.49; H, 5.05; N, 17.49. Found: C, 52.13; H, 5.03; N, 17.45.

9-(5-Deoxy-β-D-ribofuranosyl)-purine (5′-Deoxynebularine) (XI). From the Blocked Nucleoside (XIII).—A solution of 320 mg. (1 mmole) of XIII in 15 cc. of absolute methanol containing 0.2 cc. of *N* methanolic sodium methoxide was allowed to reflux for 30 minutes. The alkaline solution was evaporated *in vacuo* and the residue was dissolved in hot ethyl acetate containing just enough methanol to effect solution. The solution was kept at the b.p. for some minutes and was then cooled. The small amount of inorganic precipitate which formed was removed by filtration and the filtrate was evaporated under reduced pressure to yield 277 mg. of gummy residue. This was crystallized and then recrystallized from ether–methylene chloride and there was obtained 60 mg. (25%) of solid, m.p. 113–115°. For analysis, the substance was recrystallized once more from the same solvent system; 41 mg., m.p. 115–116°; $[\alpha]^{25}D$ −38.2° (*c* 1.83 in ethanol); $\lambda_{max}^{ethanol}$ 263 mμ (ε 5670 in acid), 264 mμ (ε 7080 in ethanol), 264 mμ (ε7170 in base).[31] The corresponding values for nebularine (9-β-D-ribofuranosylpurine) are: $[\alpha]^{20}D$ −47.3° (*c* 1 in water)[20]; λ_{max} 263 mμ (ε, 5900 in 0.1 *N* HCl)[17]; 263 mμ (ε 6900 in water)[20]; 263 mμ (ε 7100 in 0.1 *N* NaOH).[17]

From 6-Chloro-9-(5-deoxy-β-D-ribofuranosyl)-purine (XII).—To a solution of 270 mg. (1 mmole) of XII in 43 cc. of water was added 98 mg. of 10% palladium-on-charcoal catalyst and 40 mg. of magnesium oxide[17] and the stirred mixture was hydrogenated at atmospheric pressure. Uptake of hydrogen ceased after the calculated amount had been absorbed (75 minutes). The mixture was filtered through Celite and the filtrate was evaporated under reduced pressure to afford 271 mg. of glass. This was dis-

(36) This is taken as evidence for the fact that the 75 minute heating period with methanolic sodium methoxide caused complete removal of the N-benzoyl group.

(37) It is of interest that practically no separation of these anomeric mixtures could be achieved by paper chromatography in a wide variety of solvent systems.

solved in hot chloroform containing only enough methanol to bring about solution. A small amount of gummy solid precipitated on cooling and was removed. The filtered solution was evaporated *in vacuo* and the residue was crystallized and recrystallized from ether–methylene chloride. There was obtained 69 mg. (29%) of solid, m.p. 115–116°. Admixture of the solid obtained in the previous experiment did not depress the m.p. The ultraviolet and infrared spectra of the two solids were identical.

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Tertiary Hydroxyl Group Elimination in Steroid Ketols[1]

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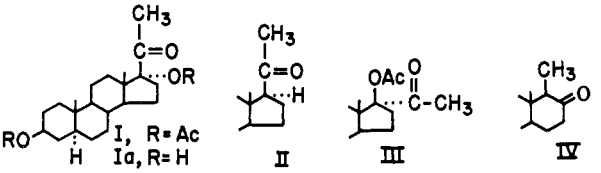
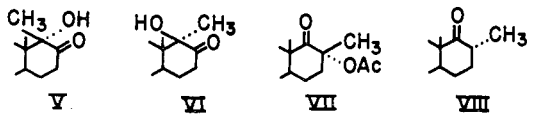
3β,17α-Diacetoxyallopregnane-20-one (I) reacted with zinc dust in refluxing glacial acetic acid to form 3β-acetoxyallopregnane-20-one (II) in 89% yield while 3β,17β-diacetoxyallopregnane-20-one (III) afforded 46% of II. Under identical conditions, 3β,17α-dihydroxyallopregnane-20-one (Ia) yielded 8% of II and 14% of 3β-acetoxy-17αβ-methyl-D-homoandrostane-17-one (IV). In the 17a-hydroxy-17-ketones, 3β-acetoxy-17aα-hydroxy-17aβ-methyl-D-homoandrostane-17-one (V) reacted with zinc–acetic acid to form 78% of IV while the 17aβ-hydroxy epimer VI was recovered unchanged. 3β,17α-Diacetoxy-17β-methyl-D-homoandrostane-17a-one (VII) yielded 88% of 3β-acetoxy-17α-methyl-D-homoandrostane-17a-one (VIII) under the same conditions. The results are discussed in terms of the conformation of the tertiary hydroxyl groups.

Treatment of steroid ketols or ketol acetates with divalent metals under reducing conditions has been shown to be an effective method for the removal of the hydroxyl or acetoxyl function provided a double bond, halogen atom or additional acetoxyl, is attached to a carbon alpha to the ketol structure.[2] Under these conditions, the ketone group is largely unattacked. However, when no such additional groups are present, deacetoxylation in good yield is dependent upon the steric requirements of the reaction. Thus, in ring C ketol ace-





tates of the bile acid series deacetoxylation proceeds in almost quantitative yields when these substances are refluxed with zinc dust in glacial acetic acid provided the acetoxyl function occupies the axial position, but in less than 30% yield when this group has the equatorial conformation.[3] Similar results were reported by Chapman, Elks, Phillips and Wyman[4] who found that in the preparation of 11-oxotigogenin, the corresponding 12α-acetoxy (axial) compound was more easily deacetoxylated with barium or calcium in liquid ammonia than was the epimeric 12β-compound. These results have been interpreted in the light of investigations of Barton and his group[5] who have shown that 1,2-eliminations takes place with greater ease if the substituents are coplanar, *trans* and axial.[3]

The epimeric 17-acetoxy-20-ketosteroids represent further examples of ketol acetates which should deacetoxylate in a way that would be influenced by the conformation of the acetoxyl group. Although the 17-acetoxyl group is attached to a 5-membered ring, inspection of molecular models shows that the 17α-acetoxyl is perpendicular to the D ring and is axial while the 17β-acetoxyl group is equatorial and lies almost in the plane of ring D. When 3β,17α-diacetoxyallopregnane-20-one (I)[6] was refluxed for 24 hours with zinc dust and glacial acetic acid, 3β-acetoxyallopregnane-20-one (II) was obtained in 89% yield accompanied by about 8% of the starting material. Under the same conditions, the epimeric 3β,17β-diacetoxyallopregonane-20-one (III) afforded 46% of 3β-acetoxyallopregnane-20-one (II) and 45% of the starting material III was recovered. It should be noted that inversion of the acetyl side chain had taken place in the formation of 3β-acetoxyallopregnane-20-one (II) from III while in the conversion of I to II the configuration occupied by the side-chain was unaffected. In both cases, no trace of the 17-epimer of 3β-acetoxyallopregnane-20-one was detected in the reaction products. This is explained by the formation of a common intermediate represented as an enol-zinc complex

(1) This investigation was supported in part by a grant from the American Cancer Society and a research grant (C-440) from the National Cancer Institute of the National Institutes of Health, United States Public Health Service.

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