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CARBOCYCLIC ANALOGS OF 2'-DEOXYADENOSINE AND 3'-DEOXYADENOSINE

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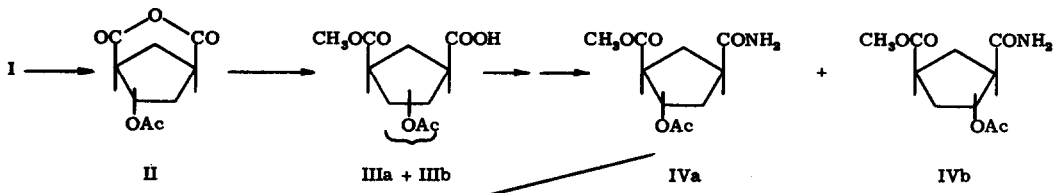
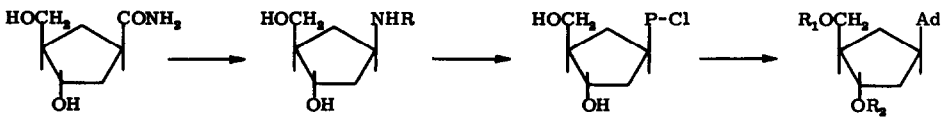
The continuing interest in analogs of the nucleoside constituents of ribonucleic and deoxyribonucleic acids has stimulated syntheses of a large number of such compounds and numerous studies of their biological properties. Interesting biological effects may be produced by modifications in the structures of either the base or the furanose moiety (1). Replacement of the tetrahydrofuran ring by a cyclopentane ring has given racemic carbocyclic analogs of thymidine (2), adenosine (3,4), inosine (4), and other purine nucleosides (4). Subsequently, the structure of the antibiotic aristeromycin (5) was determined by X-ray crystallography to be the D-isomer of the carbocyclic analog of adenosine (6), a finding that enhances interest in carbocyclic analogs. We now report the synthesis of the racemic carbocyclic analogs of 2'-deoxyadenosine and 3'-deoxyadenosine (cordycepin).

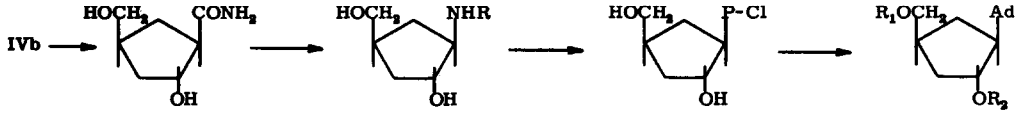
Oxidation of exo-5-norbornen-2-ol acetate (7) with sodium permanganate gave (±)-trans-4-acetoxy-cis-1,3-cyclopentanedicarboxylic acid (I), mp 116-117°, (recrystallized from EtOAc-hexane) (8), and treatment of I with acetic anhydride gave the cyclic anhydride (II, mp 117-118°; ir bands at 1740, 1775, 1815 cm^{-1}). Opening of the anhydride ring of II with nucleophiles produces two positional isomers. The mixture of monomethyl esters (IIIa and IIIb) obtained by treatment of II with methanol was treated first with thionyl chloride and then with ammonia in order to obtain a mixture of methyl (±)-trans-2- (IVa) and (±)-trans-3-acetoxy-cis-4-carbamoylcyclopentanecarboxylate (IVb). One positional isomer, subsequently identified as IVa (mp 108-109°), crystallized from benzene; the other (IVb, mp 73° and 80°) was isolated by chromatography on silica gel. The following sequence of steps yielded (±)-cis-4-amino-trans-2-hydroxycyclopentanemethanol (VIIa): reduction of IVa with $LiBH_4$ in tetrahydrofuran to Va (crystallized from EtOH-benzene, mp 127-128°), conversion of Va to the methyl carbamate (VIa, mp 89° after chromatography on silica gel in 5:1 $CHCl_3$-CH_3OH) by a Hofmann hypobromite reaction in methanol, and acidic hydrolysis of VIa to VIIa. The amine (VIIa) was isolated and purified by chromatography on a cation-exchange resin and was obtained as an analytically pure syrup (67% yield) that crystallizes at low temperatures.

Interaction of VIIa and 5-amino-4,6-dichloropyrimidine furnished the pyrimidinyl derivative VIIIa: mp 180° (recrystallized from EtOAc-EtOH-hexane); uv max. in nm ($\epsilon \times 10^{-3}$) at 308 (12.8) at pH 1, 264 (8.8) and 292 (9.5) at pH 7 and at pH 13. Treatment of VIIIa with triethyl orthoformate and hydrochloric acid gave the crude 6-chloropurine (IXa) hydrochloride, which was converted with ammonia to (±)-9-[trans-3-hydroxy-cis-4-(hydroxymethyl)-cyclopentyl]adenine (Xa). Chromatography on a cation-exchange resin and recrystallization from EtOAc-EtOH gave pure Xa: mp 189-190°; uv max. in nm ($\epsilon \times 10^{-3}$) at 259 (14.2) at pH 1, 262 (14.7) at pH 7 and at pH 13.


I
II
IIIa + IIIb
IVa
IVb


Va
VIa, R = -COOCH3
VIIa, R = H
VIIIa, R =
IXa
Xa, R1 = R2 = H
XIa, R1 = Trityl, R2 = H
XIIa, R1 = Trityl, R2 = Acetyl
XIIIa, R1 = H, R2 = Acetyl
XIVa, R1 = Tosyl, R2 = Acetyl


Cl-P =
Ad =


IVb
Vb
VIb, R = -COOCH3
VIIb, R = H
VIIIb, R =
IXb
Xb, R1 = R2 = H
XIb, R1 = Trityl, R2 = H
XIIb, R1 = Trityl, R2 = Acetyl
XIIIb, R1 = H, R2 = Acetyl
XIVb, R1 = Tosyl, R2 = Acetyl

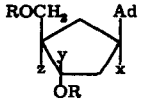

C7H7SO3
XVa
C7H7SO3
XVb

That the initial cis-relationship of the functional groups undergoing transformation from I → Xa was preserved in the hydroxymethyl and adenine groups of Xa was confirmed by preparing the cyclic derivative XVa, which is an analog of the cyclonucleoside of 2'-deoxyadenosine, by the following sequence of steps: (1) tritylation of Xa to XIa (recrystallized from EtOAc, mp 225°); (2) acetylation of the secondary hydroxyl group to XIIa (not purified); (3) detritylation of XIIa to XIIIa (silica gel chromatography, mp 132–135°) with 80% acetic acid; (4) tosylation of XIIIa and heating of the tosylate (XIVa) to effect cyclization to XVa (mp 283–286° dec.; uv max. in nm ($\epsilon \times 10^{-3}$) at 272 (15.1) at pH 1 and at pH 7, 272 (8.2) at pH 13).

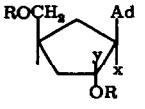
The same route was employed in the synthesis of (±)-9-[trans-2-hydroxy-cis-4-(hydroxymethyl)cyclopentyl]adenine (Xb) from IVb, and experimental conditions for preparing and isolating the following intermediates were similar to those used for Series a: Vb (mp 123–124°); VIb (mp 78–79° and 100–102°); VIIb (syrup, not purified); VIIIb (mp 183–185°, uv data essentially the same as those for VIIIa); IXb hydrochloride (converted without purification to Xb). The adenine derivative (Xb), after elution from a column of cation-exchange resin, was recrystallized from EtOH: mp 224–225°; uv max. in nm ($\epsilon \times 10^{-3}$) at 259 (14.0) at pH 1, 262 (14.4) at pH 7 and at pH 13.

The steps listed for the conversion of Xa to the cyclic derivative XVa were also carried out in order to confirm the cis-relationship of the adenine and hydroxymethyl groups of Xb: XIb (mp 226°); XIIb (not purified); XIIIb (mp 186–187°; uv max. in nm ($\epsilon \times 10^{-3}$) at 258 (14.3) at pH 1, 262 (14.7) at pH 7 and at pH 13); XIVb (not purified). The cyclic derivative obtained from the tosylate XIVb melted at 243–246° dec.; uv max. in nm ($\epsilon \times 10^{-3}$) at 272 (15.2) at pH 1 and at pH 7, 271 (8.1) at pH 13.

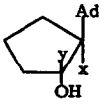
The assignment of structures to the two adenine derivatives (Xa and Xb) and to their precursors, beginning with the first separated pair of isomers (IVa and IVb), is based on two lines of evidence: (1) a sharp distinction in the behavior of the two aminodiols (VIIa and VIIb) toward periodate and (2) evidence provided by nmr spectra of the adenines Xa and Xb. The two aminodiols were treated with 0.94 equiv. of sodium periodate (citrate buffered), and unconsumed periodate was determined at intervals by the method of McCasland and Smith (9). The aminodiol derived from the ester-amide (polymorphic) with melting points of 73° and 80° consumed periodate rapidly (75% within 10 min., 99% within 190 min.); the aminodiol derived from the ester-amide with mp 108–109° did not consume periodate (beyond the experimental error of the method) during longer periods (up to 330 min.) of exposure. The amide-ester with mp 73° and 80° is, therefore, IVb, and the series of compounds obtained from it are as shown (Vb–XVb). Correspondingly, the ester-amide with mp 108–109° is IVa, and its derived compounds are Va–XVa.



Xa, R = H
XVIa, R = $-COCF_3$



Xb, R = H
XVIb, R = $-COCF_3$



XVII

The nmr multiplets (10) of protons x and y of Xa in DMSO-d_6 were clearly distinguishable and appeared at ca. 4.18 (y) and (after addition of D_2O) at ca. 5.1 (x). In contrast, the x and y multiplet of Xb strongly resembled that of the model cyclopentyladenine (XVII) with an hydroxyl group adjacent to the adenine ring; the x and y protons of both compounds produced an overlapping multiplet centered at ca. 4.5. More importantly, trifluoroacetylation of both hydroxyl groups of Xa and Xb occurred in trifluoroacetic acid, and the chemical shifts of protons x and y of XVIb were then separated multiplets centered at ca. 5.37 and 5.98. Spin-decoupling experiments with XVIb showed spin-spin coupling between x and y of a magnitude appropriate for vicinal protons. Evidence that y and z of XVIa are vicinal was obtained by spin-decoupling after the approximate chemical shift of z was determined by decoupling from $-CH_2OCOCF_3$.

Thus, both the periodate determinations and nuclear magnetic resonance data are consistent with the depicted structures (11,12).

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8. Dimethyl (+)-trans-4-hydroxy-cis-1,3-cyclopentanedicarboxylate has been prepared by ozonolysis of (+)-exo-5-norbornen-2-ol acetate: R. K. Hill, P. J. Foley, Jr., and L. A. Gardella, J. Org. Chem., 32, 2330 (1967).

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10. Nmr peak positions are in ppm downfield from internal tetramethylsilane (δ scale).

11. Structures shown in this communication depict only one isomer of an enantiomeric pair.

12. Analytical data were satisfactory for specimens of compounds I, II, IVa-VIIIa, Xa, XIa, XIIIa, XVa, IVb-VIb, VIIIb, Xb, XIb, XIIIb, XVb. Specimens in KBr discs were used for ir determinations.