tor controlled heater baths. Temperatures were measured with a National Bureau of Standards calibrated thermometer.

The experimental values for $5C_3F_7COOH\cdot3C_6H_5N(CH_3)_2$ were 43.85 centistokes (cts.) at 21.0°, and 6.867 cts. at 67.55°. After standing for 120 days the measured viscosity was 52.60 cts. at 17.7°. All these values lie on a straight line when plotted on an ASTM (D 341-39 and 43) viscosity chart, and the following values were read off this line in centistokes: 210 (0°), 35.0 (25°), 11.0 (50°), 5.1 (75°) and 2.9 (100°). The slope of this line, showing the temperature dependence of viscosity, i.e., the so-called ASTM slope was 0.93.

The experimental values for $2C_3F_7COOH\cdot(C_2H_5)_2O$, in cts., were 1.318 at 21.0° and 0.634 at 67.55°. The viscosities for rounded temperature values were taken from the ASTM line: 2.20 cts. (0°), 1.22 (25°), 0.80 (50°), 0.58 (75°), 0.46 (100°). The ASTM slope was 1.19.

A Phospho-tri-anhydride Formula for the Nucleic Acids

BY EDWARD RONWIN[1]

A new structural formula for both ribo- and desoxyribo-nucleic acids is proposed, having as its core a $(P_2O_5)_n$ polymer chain of phospho-anhydride links. There are three such links per P atom. In addition, each P atom binds one hydroxyl group and one nucleoside (in a phospho-sugar ester bond). A unit cell, based on the proposed formula for the nucleic acids, is calculated. By means of a theoretical treatment, the formula is shown to be compatible with the available, factual data concerning the structure of the nucleic acids.

A careful examination of the available data concerning the structure and behavior of the nucleic acids leads to the conclusion that the facts are consistent with only *one* phospho-sugar ester bond per nucleotide and that the basic structure of the nucleic acids is a polymer core of phospho-anhydride links. There are three such links per phosphorus atom. In addition, each phosphorus atom binds one hydroxyl group and one nucleoside (phospho-sugar ester link) as shown diagrammatically in Fig. 1 for a ribose nucleic acid type (the difference between ribose and desoxyribose types will be discussed later.)

Section E, Fig. 1 represents an end group of the polymer chain. Its basic tetrahedral structure is identical with that of the hexagonal (monomeric)

form of P_4O_{10}.[2-5] This can be visualized by mentally replacing all OH and ONu groups bound to each phosphorus atom by a single oxygen atom engaged in an "apical" $P{\equiv}O$.[3,6,7]
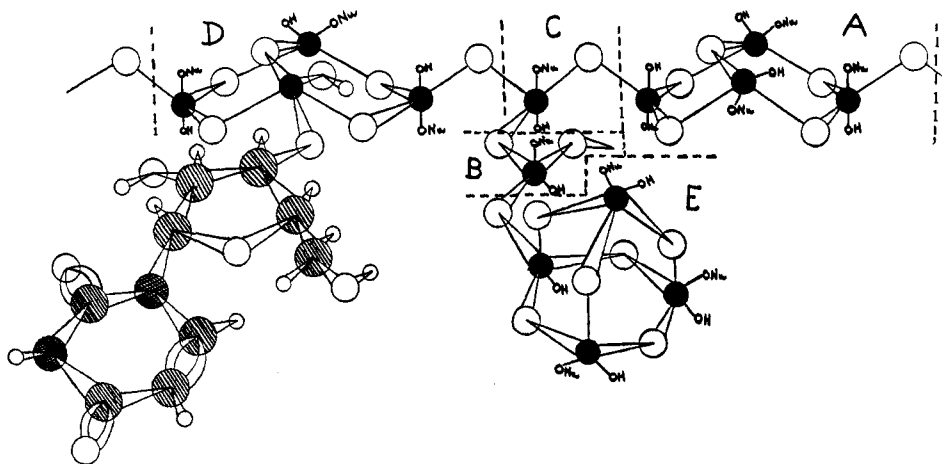

Fig. 1.—Proposed new structure for the nucleic acids: ●, phosphorus atoms; O, oxygen atoms; ●, carbon atoms; ●, nitrogen atoms; ONu, o-nucleoside (phospho-sugar ester link); °, hydrogen atoms. Bond distances, bond angles and relative atom and group sizes are not depicted exactly. To obtain proper perspective of the relationship between the polymer chain and the nucleoside, the uridine nucleoside should be considered as rotated 90°. The base of the nucleoside is to be imagined as parallel to the sugar moiety, but extending back toward the polymer core.

nucleotide and that the basic structure of the nucleic acids is a polymer core of phospho-anhydride links. There are three such links per phosphorus atom. In addition, each phosphorus atom binds one hydroxyl group and one nucleoside (phospho-sugar ester link) as shown diagrammatically in Fig. 1 for a ribose nucleic acid type (the difference between ribose and desoxyribose types will be discussed later.)

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By cleavage of the proper P–O–P bond, section E can be opened to form a unit which is identical to the equivalent sections A and D. Sections B and

(2) W. L. Hill, G. T. Faust and S. B. Hendricks, THIS JOURNAL, **65**, 794 (1943).

(3) G. C. Hampson and A. J. Stosick, *ibid.*, **60**, 1814 (1938).

(4) L. R. Maxwell, S. B. Hendricks and L. S. Deming, *J. Chem. Phys.*, **5**, 626 (1937).

(5) H. C. J. DeDecker and C. H. MacGillavry, *Rec. trav. chim.*, **60**, 159 (1941).

(6) The "apical" P to O bond in any of the forms of P_4O_{10} has been found to possess a bond distance of 1.39 Å.[3,7] Addition of the triple bonding radii for P and O yields 1.43 Å. Hence, this bond, having a calculated bond energy of 237.9 kcal./mole, may appropriately be referred to as a triple bond.

(7) H. C. J. DeDecker, *Rec. trav. chim.*, **60**, 413 (1941).

(1) Present mailing address: Room 1557, Div. of Biochemistry, L. S. Bldg., Univ. of Calif., Berkeley 4, California.
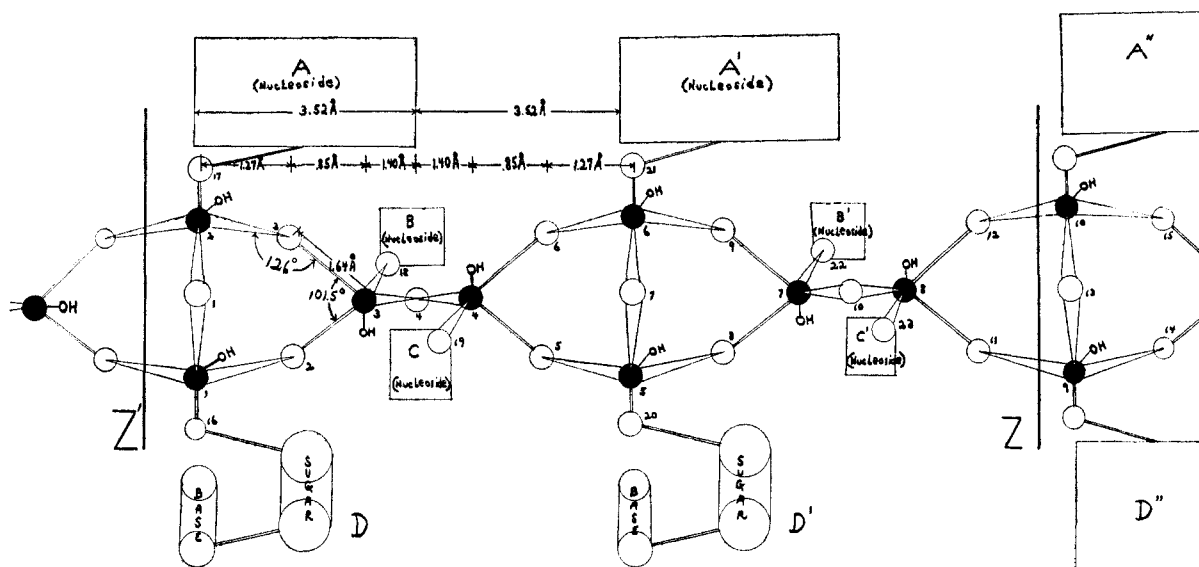
Fig. 2.—Top view of a unit cell of a nucleic acid polymer chain: O, oxygen atoms; ●, phosphorus atoms.

C, which illustrate branching possibilities, can both be replaced by any number of units such as section A.

Replacing all OH and ONu groups on every P atom of section A (or D) with a single, apical P≡O leads to a $(P_2O_5)_n$ polymer which, though the data accumulated are limited,[2] appears to be identical with the "tetragonal" form of "P_2O_5." The polymeric, tetragonal form is prepared by heating the monomeric, hexagonal form, a structural change analogous to the section E, P–O–P bond cleavage to form polymeric units such as sections A or D.

The essential difference between the proposed nucleic acid polymer and the tetragonal $(P_2O_5)_n$ polymer is that each P≡O of the $(P_2O_5)_n$ polymer appears to be replaced by a P–O–H[8] and a P–O–nucleoside bond[8] in the nucleic acids. This can attain reality; for example, in vivo, by the hydration of the P≡O bonds followed by esterification with a nucleoside, a process favored by energy considerations. Further, the polymerization to $(P_2O_5)_n$ or to the proposed nucleic acid polymer core is not a spontaneous process; hence, the converse should be true. This is confirmed by the well known spontaneous degradation of nucleic acids when standing in neutral solutions over a short period of time.[9]

In Fig. 2,[10] it will be noted that the length of a nucleic acid unit cell (defined by Z to Z') containing eight nucleotides (≅ four P_2O_5 units) is 14.0 Å. Every "P_2O_5" section of the proposed nucleic acid chain, containing two "average" nucleosides and two hydroxyl groups, has an "average" molecular weight of 662. Using the density of the nucleic acid as 1.63,[11] a value of 2,700 Å.[3] is obtained for the volume of the unit cell of the nucleic acids. Since the length is 14.0 Å., the product of the width and thickness is 193 sq. Å. Figure 3 represents the

(8) The same phosphorus atom is involved in both bonds.
(9) C. F. Vilbrandt and H. G. Tennent, THIS JOURNAL, **65**, 1806 (1943).
(10) The P–O–P bond distances and bond angles shown in Fig. 2 are based on those previously determined for the monomeric[3,4] and orthorhombic (polymer)[7] forms of P_4O_{10} (in both of which they are identical).
(11) W. T. Astbury, Symposia Soc. Expt. Biol., **1**, 66 (1947).

unit cell of the nucleic acids. The smaller rectangle depicts the actual area covered by the polymer core itself. Its width is 2.80 Å. and its thickness is 1.88 Å. From this core extend the "average" nucleosides. Since they are "average" nucleosides, $\frac{X}{2} = \frac{Y}{2}$. Hence: $\left(\frac{2X}{2} + 2.80\right)\left(\frac{2Y}{2} + 1.88\right)$

= 193 sq. Å. which yields a value of 5.8 Å. for $\frac{X}{2}$ (or $\frac{Y}{2}$). Therefore, the nucleosides extend from the core to a distance of no more than 5.8 Å. Since this distance is nearly that which would be covered by the sugar moiety protruding from the sides of the polymer core, the basic portion of the nucleosides must be bound to the sugar so as to "fold under" the sugar moiety and extend back toward the core. This helps to create the compact and dense units that the nucleic acids are known to be. From the preceding, the dimensions of the nucleic acid unit cell become, approximately: length, 14.0 Å., width, 14.5 Å., and thickness, 13.5 Å. It is inter-
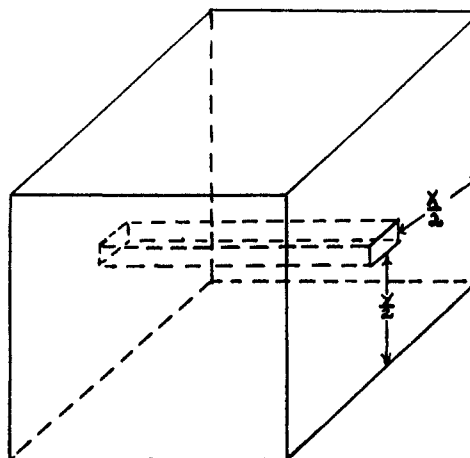

Fig. 3.—Simplified version of a unit cell of a nucleic acid containing average nucleotides.

esting that Astbury and Bell[12] find by X-ray analysis that a principal side spacing equaled 16.2 Å.

Figure 2 will also assist in the ensuing consideration of X-ray data. In the diagram only the bonds of the chain have a relative proportionality to each other; the exact bond angles are not shown. It should be noted that the bond distance between P_3 and O_4 is 1.64 Å.; however, it is angular so that when perpendiculars are dropped to the plane of the paper, the distance becomes 1.40 Å. The bonds of the nucleosides through the oxygen atom of the sugar moiety to the P atom of the chain are only approximations. The OH group attached to every P atom bears no size, bond distance or angle relationship to reality.

X-Ray data indicate that the purines and pyrimidines are flat and parallel to the flat sugar rings, but not coplanar with the sugar moieties owing to their bonding at an angle.[12] Both, in turn, are perpendicular to the long axis of the chain.[11,13,14] The flat requirement for the sugar moiety prescribes the furanose type and the base to sugar linkages must all be either alpha or beta. From Fig. 2, it is readily seen that these requirements are fulfilled by the proposed structure.

Astbury[12] reported a regular repeated pattern involving eight nucleotides or a multiple of eight, such as sixteen. The unit cell of Fig. 2 (Z to Z') defines just such a pattern. It should be noted that whereas the P_3-O_4-P_4 bond is below the plane of the paper, the P_7-O_{10}-P_8 is above the plane of the paper. This difference in linkage creates the unit cell of eight nucleotides.

The nucleotides appear to lie "one on top of another."[12] The nucleosides D, D' and D" and A, A' and A" (Fig. 2) are to be considered as extending half above and half below the plane of the paper. Nucleosides B and B' (drawn small so as to avoid confusing the diagram) are extending perpendicularly to P_3 and P_7 below the plane of the paper; whereas nucleosides C and C' extend perpendicularly to P_4 and P_8 above the plane of the paper. All nucleosides have their long axis perpendicular to the long axis of the polymer chain. Looking down from Z to Z' (Fig. 2), the nucleosides will appear flat and will lie "one on top of each other." They will extend out from the chain in four rows whose long axis will cross at right angles to each other in the center of the polymer core. Figure 4 illustrates the effect.

The distance between nucleotides was reported as about 3.5 Å. and their effective thickness as 3.4 Å.[11,12] If the nucleosides join the chain at the phosphorus atoms as indicated in Fig. 2, the distance separating them would be about 3.5 Å., and their effective thickness would also be about 3.5 Å. These values (only approximations) are in good agreement with Astbury's reported values.[11,12] It must be remembered that the exact angles of bonding of the nucleosides and the OH groups on the phosphorus atoms are, as yet, not known.

(12) W. T. Astbury and F. O. Bell, Cold Springs Harbor Symposia Quant. Biol., 6, 109 (1938).

(13) A. Butenandt, H. Friedrich-Fresksa, S. Hartwig and G. Scheibe, Z. physiol. Chem., 274, 276 (1942).

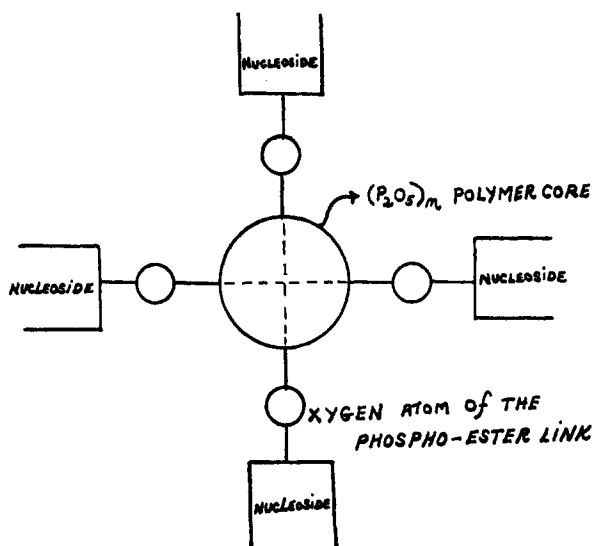(14) S. S. Cohen and W. M. Stanley, J. Biol. Chem., 144, 589 (1942).

Fig. 4.—Looking down the nucleic acid polymer chain from one end. Though the polymer core is shown as a circle it would actually appear rectangular. The bond distances shown bear no relation to reality.

The phospho-tri-anhydride formula requires only one phospho-sugar ester linkage per nucleotide. The difficulty of reconciling the internucleotide distance (2.5 Å.) obtained by employing the known O-P-O bond angles and distances with the internucleotide distances obtained by X-ray analysis (3.5 Å.) has caused Astbury[11] to rule out a C(2) to C(3) diphosphoester linkage for the nucleic acids. A C(3) (or C(2)) to C(5) diphosphoester linkage may exist; these linkages, however, are incompatible with the known stability of 5-phosphonucleotides under alkaline conditions which utterly destroy ribose nucleic acids. The recent findings by Cohn and Volkin[15] of 5-phosphonucleotides in enzyme digests of calf-liver ribonucleic acid does not establish a C(3) (or C(2)) to C(5) diphospho-ester link and is in no way incompatible with the proposed formula since (see Fig. 1) the sugar may be bound in the one phospho-ester link per nucleotide at either C(2) or C(3) or C(5) in ribose nucleic acids and at C(3) or C(5) in the desoxyribose varieties.

Ether linkages[16,17] and phosphoamide linkages[18,19] previously proposed have been discarded.[19-21] The formula postulated herein requires neither of these discredited linkages for its existence.

Thus, from X-ray considerations which favor only one phospho-sugar ester bond per nucleoside, by elimination of ether (sugar-sugar) linkages and by the elimination of phosphoamide linkages (phosphoryl-base and base-base linkages), the internucleotide linkages have been narrowed to only one possible type: inter phospho-anhydride links, as indicated in the postulated formula.

Though the commercial product, "P_2O_5" (the

(15) W. E. Cohn and E. Volkin, Nature, 167, 483 (1951).

(16) W. Jones and M. E. Perkins, J. Biol. Chem., 55, 557 (1923).

(17) W. Jones and B. E. Read, ibid., 29, 111, 123 (1917).

(18) H. Bredereck and G. Richter, Ber., 69, 1129 (1936).

(19) P. A. Levene and W. A. Jacobs, ibid., 43, 3150 (1910).

(20) H. Bredereck, E. Berger and F. Richter, ibid., 74, 338 (1941).

(21) H. Bredereck, M. Koethnig and G. Lehmann, ibid., 71, 2613 (1938).

hexagonal, monomeric form) reacts with water in a violent manner, the polymeric forms react much more slowly with water, yielding suspensions and gels of varied polymeric composition.[2] Bearing in mind the presence of nucleosides in the nucleic acids, their behavior toward water is somewhat similar to that of the polymeric forms of "P_2O_5."

The *polymerized* acids are generally agreed to be tetra-basic per four phosphorus atoms.[22][24][26] That is, every phosphorus atom carries a primary titratable dissociation. As shown in Figs. 1 and 2, every phosphorus atom in the proposed formula is bound, in addition to the –O-nucleoside linkage, to a hydroxyl group, which would yield a primary dissociation.

Due to the heterogeneous nature of the degradation products, many titration results, reporting the existence of varying numbers of primary and secondary dissociations per four phosphorus atoms, represent meaningless averages.[26]

(22) J. M. Gulland, *J. Chem. Soc.*, 1722 (1938).
(23) F. W. Allen and J. J. Eiler, *J. Biol. Chem.*, 187, 757 (1941)
(24) E. Hammarsten, *Biochem. Z.*, 144, 383 (1924).
(25) Z. Makino, *Z. physiol. Chem*, 236, 201 (1935); 232, 229 (1935).
(26) F. Schlenk, *Advances in Enzymol.*, 9, 512 (1949).

The proposed formula permits any sequence and ratio of nucleosides and need not conform to the "tetranucleotide" concept, which has been challenged by Gulland, *et al.*,[27]

Astbury[11] offers data which indicates that ribosenucleic acids and the desoxyribose varieties are very similar in structure. By replacing the uridine nucleoside in Fig. 1 by any nucleoside common to desoxyribose nucleic acids, the proposed structure is converted from the ribose to the desoxyribose types.

The recent work of Carter[28] points toward the establishment of C(5) as the site of the *one* phosphosugar ester link per nucleoside in thymus desoxyribonucleic acid. However, C(3) is still not excluded as a point of linkage and in some desoxyribose nucleic acids a portion of the nucleosides may be linked at C(5) while the others are at C(3).

Finally, the author wishes to express his appreciation to Drs. C. A. Knight and Frederick H. Carpenter for their criticism of this paper.

(27) J. M. Gulland, D. O. Jordan and C. J. Threlfall, *J. Chem. Soc.*, 1129 (1947).
(28) C. E. Carter, THIS JOURNAL, 73, 1537 (1951).

[CONTRIBUTION FROM THE RESEARCH LABORATORY, DOMINION RUBBER CO. LTD.]

The Alkaloids of Fumariaceous Plants. XLVII. The Structure of Coreximine

BY RICHARD H. F. MANSKE AND WALTER R. ASHFORD

Coreximine has been shown to be 2,9-dimethoxy-3,8-dihydroxytetrahydroprotoberberine by a synthesis of its O,O-diethyl ether which was identical with the racemized diethyl ether of the natural alkaloid.

Coreximine has recently been shown to yield norcoralydine (I) on O-methylation with diazomethane.[1] Since it contains two hydroxyls, four structures are possible if vicinal hydroxyls are excluded. It was relatively easy to locate the position of the hydroxyl in the upper left hand

I, R = Me
II, R = H
III, R = Et
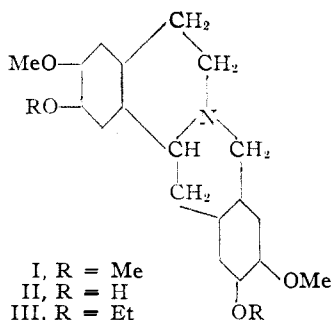
nucleus shown in the formula (I). Mild oxidation of the O,O-diethyl ether with permanganate yielded 1-keto-6-methoxy-7-ethoxytetrahydroisoquinoline. One of the hydroxyls in coreximine is therefore in the 7-position of the isoquinoline systems. Further oxidation however could yield only 4-methoxy-5-ethoxyphthalic acid regardless of the location of the original hydroxyls and this acid was the only one obtained experimentally.

(1) R. H. F. Manske, THIS JOURNAL, 72, 4796 (1950).

There remained therefore only two possible structures for coreximine and it seemed most probable that ring closure of the benzylisoquinoline by condensation with a formaldehyde equivalent would only proceed if the hydroxyl were para to the position of attack. On this basis coreximine should be II and this supposition was confirmed by a synthesis of the compound III, which proved to be identical with a specimen of racemized coreximine O,O-diethyl ether.

The synthesis followed the well-known routes by which benzylisoquinolines may be obtained. The necessary β-dialkoxyphenethylamine is a well known compound[2] and was prepared by the details given by Fluchaire and Chambret[3] and the 3-ethoxy-4-methoxyphenylacetic acid[4] was prepared by a series of reactions detailed by Kindler and Peschke[5] for the dimethoxy analog. The combination of these two fragments to the necessary amide prior to ring closure was effected in quantitative yield by heating them in tetralin[6] and the subsequent reactions leading to 1-(3-ethoxy-4-methoxybenzyl) - 6 - methoxy - 7 - ethoxytetrahydroisoquinoline and the final ring closure with form-

(2) G. Barger, J. Eisenbrand, L. Eisenbrand and E. Schlittler, *Ber.*, 66, 450 (1933).
(3) Fluchaire and F. Chambret, *Bull. soc. chim.*, 11, 22 (1944).
(4) E. Späth and K. Tharrer, *Ber.*, 66, 583 (1933).
(5) H. Kindler and W. Peschke, *Arch. Pharm.*, 271, 431 (1933).
(6) B. I. O. S. No. 706, pl. 124.