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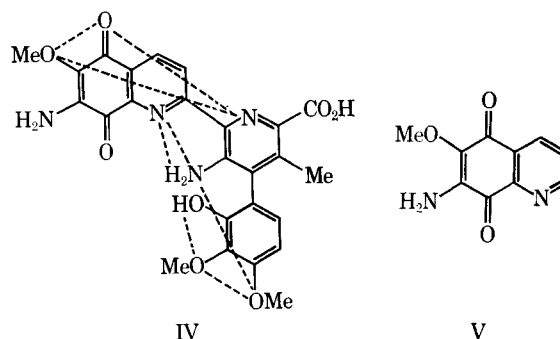
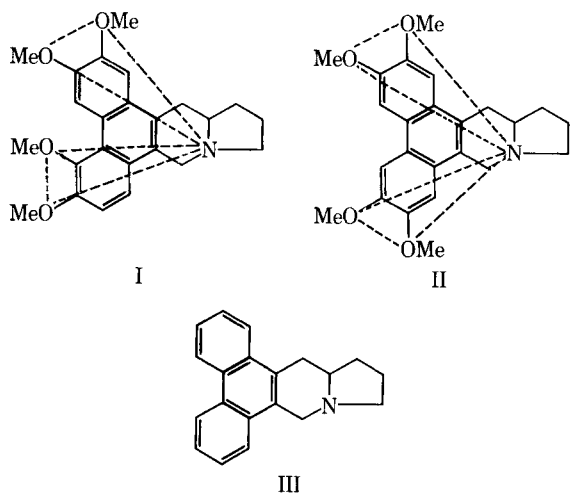
Common Receptor-Complement Feature among Some Antileukemic Compounds

KWANG-YUEN ZEE-CHENG and C. C. CHENG

Abstract □ A common structural feature was found among some nonalkylating antileukemic agents such as aminopterin, anthramycin, 5-azacytidine, bisketopiperazines, camptothecin, cytosine arabinoside, daunomycin, demecolcine, emetine, glutarimide antibiotics, harringtonine, 6-mercaptopurine riboside, methotrexate, sangivamycin, streptonigrin, tylocrebrine, tylophorine, vinblastine, and vincristine. This structural feature consists of a triangulation composed of one nitrogen and two oxygen atoms with rather definite interatomic distances. This structural characteristic may contribute to the *in vivo* binding to one of the pertinent receptor sites involved in leukemia geneses.

Keyphrases □ Antileukemic compounds—common receptor complement □ Structural similarity, antileukemic agents—triangular pattern, nitrogen, oxygen atoms □ Oxygen, nitrogen pattern, interatomic distances—antileukemic activity

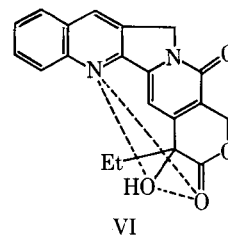
In connection with structure-activity studies of various oncolytic agents, a common structural feature was noted among a number of antileukemic agents. The purpose of this paper is to present a preliminary account of this observation.



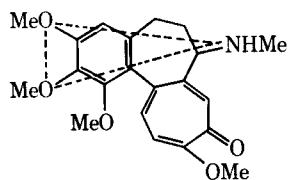
THEORETICAL

The tylophora alkaloids (1), tylocrebrine (I) and tylophorine (II), were found to possess antileukemic activity against leukemia L-1210 in mice (2). The nucleus of these alkaloids, phenanthro-[9,10:6',7']indolizidine (III) (3), however, is devoid of the activity (4) exhibited by the polysubstituted methoxy derivatives.

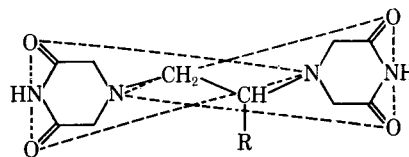
The antibiotic streptonigrin (IV), the structure of which contains an *o*-aminoquinone unit (5), exhibits a broad spectrum of inhibitory activity against a number of leukemias, lymphomas, carcinomas, and other tumor systems (6-13). Although the *o*-aminoquinone unit is also present (5) in two other types of antitumor antibiotics (mitomycin C and actinomycin D, for example), a synthetic compound, 7-amino-6-methoxy-5,8-quinolinedione (V) (14), which possesses a partial structure of this antibiotic in that it contains the *o*-aminoquinone unit, failed to retain the original antileukemic activity.¹



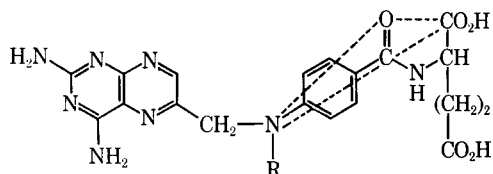
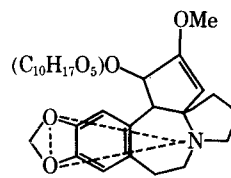
¹ Test results were provided by Dr. Harry B. Wood and Robert B. Ing of the Cancer Chemotherapy National Service Center, National Cancer Institute, U. S. Public Health Service.



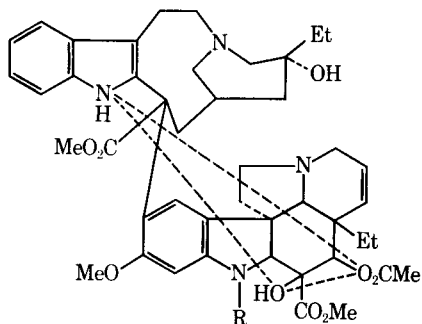
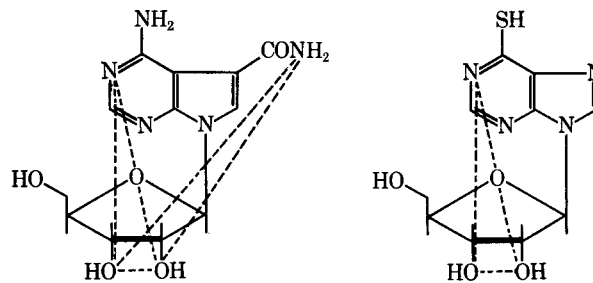
VII



XIII

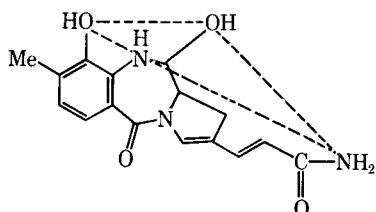
VIIIa, R = H
VIIIb, R = Me

XIV

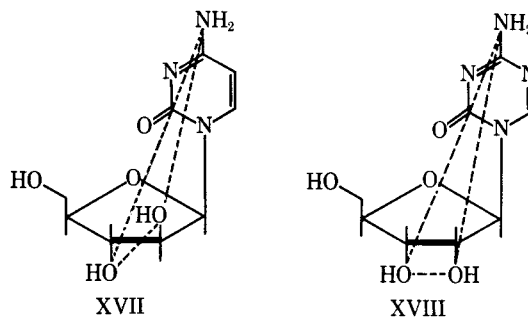
IXa, R = Me
IXb, R = CHO

XV

XVI

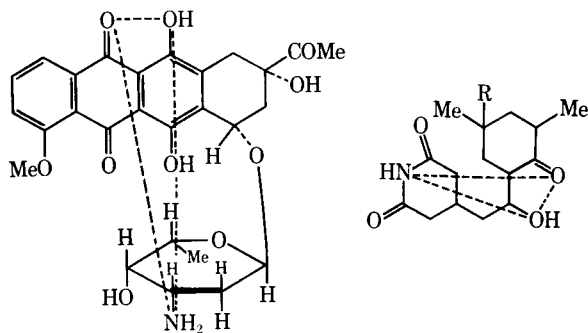


X

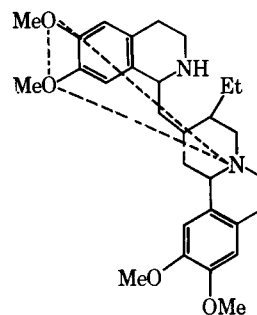


XVII

XVIII



XI

XIIa, R = H
XIIb, R = OAc
XIIc, R = OH

XIX

It has been reported that the hydroxyl and carbonyl groups presented in the lactone ring portion of camptothecin (VI) (15–19) may account for the antileukemic activity displayed by this alkaloid. Modification or replacement of these functions resulted in deprivation of its oncolytic property (15, 18, 19).

A comparative study of the structure of these compounds, using the Briegleb (20)–Stuart (21) molecular models, revealed that there is a common atomic arrangement among these very differently constituted molecules. Three electronegative atoms, containing at

least one lone pair of electrons—one nitrogen and two oxygen atoms—form a triangle with very distinct parameters. The interatomic distances are rather definite, as shown in Fig. 1.

The triangular arrangements in Compounds I, II, IV, and VI are indicated by dotted lines. It is obvious that no such relationship could be found in Compounds III and V.

This interesting observation immediately prompted an examination of the structure of other compounds with antileukemic activity (at least active *versus* L-1210). This included demecolcine (VII) (22–24); aminopterin (VIIIa) (25–28); methotrexate (VIIIb) (27) [many related compounds such as dichloromethotrexate, 2,4-diaminopyrimidine analogs of aminopterin and methotrexate, and

Table I—Interatomic Distance Measurements (Å) of Some Nonalkylating Antileukemic Compounds

Compounds	N—O ₁	N—O ₂	O ₁ —O ₂
Tylocrebrine	7.50–7.71 7.38	8.75–8.87 8.04	3.01–3.35 3.01–3.35
Tylophorine	7.50–7.71 6.84	8.75–8.87 8.04	3.01–3.35 3.01–3.35
Streptonigrin	7.37 ^a 7.37 ^a	8.71 ^a 8.71 ^a	3.05–3.35 3.05–3.35
Camptothecin	6.02–7.05	8.70–9.71	3.35
Demecolcine	7.03–7.71	8.38–8.71	3.03–3.36
Aminopterin	6.37–6.70	7.70–9.37	2.69–4.03
Methotrexate	6.37–6.70	8.03–9.03	2.69–4.03
Vinblastine	6.70	8.71	3.36
Vincristine	6.70	8.71	3.36
Anthracycline	8.04–8.36	8.71–9.05	3.01–3.35
Daunomycin	7.05–10.20	8.36–11.40	2.70
Glutarimide antibiotics	6.70–7.05	8.40–9.71	3.05–3.35
Bisketopiperazines	7.04 ^a	7.85–8.38	4.00–4.35
Harringtonine	7.04	7.90	3.08
Sangivamycin	7.05 ^a 6.70 ^a	8.70 ^a 8.70 ^a	3.40 3.40
6-MP riboside	7.55 ^a	8.70 ^a	3.05
Cytosine arabinoside	6.36–7.05	8.70–9.36	3.68–4.02
5-Azacytidine	7.05 ^a	8.70 ^a	3.03
Emetine	7.03 ^a	8.50 ^a	3.30

^a Interatomic distance of conformed conformation.

quinazoline antifolates, which can have similar triangular arrangements, also displayed antileukemic activity (29–35)]; vinblastine (IXa) and vincristine (IXb) (36–44); the methyl ether of anthramycin (X) (45–49); daunomycin (XI) (50–56); the glutarimide antibiotics cycloheximide (XIIa, actidione), E-72 (XIIb), and streptovitacin A (XIIc) (57–69); bisdiketopiperazines (XIII, R = H, CH₃) (70, 71); harringtonine (XIV) (72); sangivamycin (XV) (73–75) [toyocamycin (76), which lacks the side-chain amide group, is devoid of antileukemic activity]; 6-MP riboside (XVI) (77–80) [the active form of 6-MP riboside, as well as for 6-MP, is 6-MP ribonucleotide (80)] and related compounds (80–83); cytosine arabinoside (XVII) (84–89); 5-azacytidine (XVIII) (90–95); and emetine (XIX) (96). The interatomic distances (Table I) indicated by the dotted lines, determined from the Briegleb (20)–Stuart (21) molecular models, with minor deviations in the values of anthramycin and harringtonine, are all intriguingly within the limitations of the values shown in Fig. 1.

The relationship between the triangular pattern and antileukemic activity is further substantiated by the reports that neither daunomycinone (the aglycone of daunomycin) nor the amino sugar daunosamine possesses antileukemic activity,¹ and that the indole and indoline units of vinblastine and vincristine, when separated, are also inactive (97, 98). Triangular patterns of different sizes and shapes have been reported in explaining sites of other receptors (99–101) (the muscarinic, nicotinic, histamine, serotonin, inflammatory, etc.). Although some of the triangulations are also composed of one nitrogen and two oxygen atoms, the compounds were inactive against leukemia L-1210.¹ The interatomic distances in these cases differ markedly from those illustrated in Fig. 1.

DISCUSSION

It appears that the triangular pattern, which is present among the aforementioned antileukemic compounds of both synthetic and

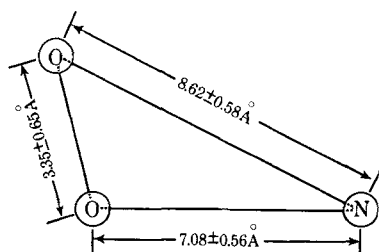


Figure 1—N—O—O triangular pattern.

natural origin, may actually contribute to one of the pertinent receptor sites (99–107) in certain biopolymers (proteins, polysaccharides, nucleic acids, etc.) involved in leukemia geneses. Thus, it may result in inhibiting the active site of the enzymes, in altering the specificity of enzyme systems, in disturbing the template molecules in transcription process, in changing the permeability of certain biological membranes, or in causing other interruptions of biological functions. Admittedly, the present observation is quite empirical, and the facts as presented are oversimplified. Additional work, such as molecular orbital calculations of preferred conformations of molecules and electron-density distribution of atoms, is definitely needed to verify the finding. Furthermore, the triangular pattern cannot be used to explain the antileukemic activity of some other compounds including hydroxyurea,² ellipticine,² and biological alkylating agents. Nevertheless, perhaps the receptor-complement feature can be used to explore the *in vivo* drug interaction in greater detail. It can also be regarded, among other considerations,³ as one of the working hypotheses in designing better and more useful antileukemic drugs.

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² Although these compounds may possibly act through different mechanisms, it is not improbable that they may undergo *in vivo* structural conversions to yield derivatives possessing the triangular characteristics.

³ For example, geometric effects, electronic effects, lipid-aqueous partition coefficients, redox potentials, basicity and acidity, and *in vivo* stability and reaction rates.

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Theoretical Justification of Reciprocal Rate Plots in Studies of Water Vapor Transmission through Films

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Abstract □ A theoretical equation has been developed justifying the graphical representation of vapor permeation data by $1/\text{rate}$ versus film thickness plots. The permeability coefficient for the film may be determined from the slope of this plot and has units in square centimeters per second. The intercept at zero film thickness is dependent upon the geometry of the experimental design and the diffusion coefficient for the vapor within the diffusion cell. The derivation of the equation assumes a nonequilibrium condition for water vapor in the diffusion cell, as well as the existence of steady-state conditions.

Keyphrases □ Water vapor—transmission through films □ Film transmission—water vapor □ Reciprocal rate plots, vapor transmission—theoretical justification □ Polymeric, unplasticized films—water vapor transmission

The passage of water vapor through polymer films, with reference to the free films having potential application as tablet film coatings, has been reported in the

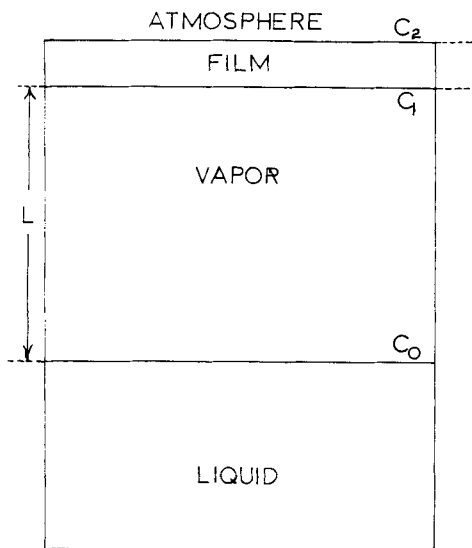


Figure 1—Schematic diagram of water vapor transmission cell depicting water concentrations existing at various surfaces. C_0 = concentration of molecules above liquid surface, C_1 = concentration of molecules at inside film surface, and C_2 = concentration of molecules at outside film surface.

pharmaceutical literature (1–3). In the first of these studies (1), a vacuum was created on one side of the film so that a pressure difference existed across the film. More recently (2, 3), the transfer of water vapor through films has been studied in which a water vapor pressure difference existed but in which the total pressure, atmospheric, was the same on both sides of the film. In these investigations (2, 3), a linear relationship was found between the reciprocal of the rate of water vapor permeation and film thickness. In one case (2), the authors stated: “An interesting relationship is observed when $(w/t)^{-1}$ is plotted against thickness of film; although no theoretical basis for such a plot can be proposed at the present time, we feel it is worth presenting.” The research described by this study and the accompanying theory present a theoretical justification for the linear relationship between the reciprocal of rate of water vapor permeation and film thickness.

THEORY

Previous investigations have used equations that relate the rate of vapor transfer to the water vapor pressure differential existing across the film. Alternatively, an expression may be used relating this rate to the concentration difference existing across the film:

$$\frac{R}{a} = \frac{PA \Delta C}{a} \quad (\text{Eq. 1})$$

where R is the rate of permeation, P is the permeability coefficient, A is the area of the film, a is its thickness, and ΔC is the water vapor concentration difference across the film. ΔC may be expressed in any suitable units such as molecules. The type of transmission cell used in previous investigations (2, 3) is shown in Fig. 1, where $\Delta C = C_1 - C_2$.

In calculating ΔC , the diffusion of water vapor from the surface of the liquid to the polymer film must first be considered. Because the distance between the liquid and the film influences the rate of water vapor transmission through the film (4), it can be assumed that the vapor pressure at the film surface is not in equilibrium with the liquid surface, and that a vapor pressure difference exists through this distance. The diffusion through this distance is given by Fick's one-dimensional equation:

$$\frac{\partial C}{\partial t} = \frac{D \partial^2 C}{\partial x^2} \quad (\text{Eq. 2})$$