17. F. Girardi, *Waste Hazard Analysis: Progress Report* (EURATOM, 1976).
18. J. Bear, *Dynamics of Fluids in Porous Media* (Elsevier, Amsterdam, 1972); J. J. Fried and M. A. Combarnous, *Adv. Hydrosci.* **7**, 169 (1971); F. W. Schwartz, *J. Hydrol.* **27-1/2**, 51 (October 1975).
19. J. Chaussidon and R. Calvet (Institut National de la Recherche Agronomique, Versaille), personal communication (1975).
20. However, interbedded permeable strata in the rock formation may transport the released elements horizontally at a larger speed and over large distances. We will not take this movement into account because if these strata were continuous and lead to the surface in the vicinity of the repository, such horizontal flow might bring the released elements much quicker to man's environment, and such a geological setting should not be considered a good repository; if these strata were discontinuous, or remained confined over great distances, this horizontal movement would only modify the position of the final outlet at the ground surface. They can be taken into account when the transient time is considered, by increasing only the thickness of the equivalent vertical formation by a factor function of the anisotropy of the permeability of the interbedded strata.
21. W. E. Prout, *Soil Sci.* **66** (No. 1), 13 (July 1958).
22. T. Tamura, *Assoc. Am. Petrol. Memo. No. 18* (1972), pp. 318–330.
23. J. M. Cleveland, *The Chemistry of Plutonium* (Gordon & Breach, New York, 1970).
24. H. Pezerat (Université Pierre and Marie Curie), personal communication (1975).
25. R. Naudet, *Bulletin d'Information Scientifique et Technique, Commissariat à l'Energie Atomique* **193** (June 1974); G. A. Cowan, *Sci. Am.* **235**, 36 (July 1976).
26. J. L. Meyer, in *IAEA/ERDA International Symposium on Transuranium Nuclides in the Environment, San Francisco, California* (November 1975).
27. J. Hamstra, *Nucl. Saf.* **16**, 2 (1975).
28. Actually, Hamstra shows that these 3530 tons of ore that are needed to produce 1 ton of fuel also produce residues, that is, mill tailings and depleted uranium-238 after enrichment. These residues need an additional 2.2×10^8 m^3 of water to dilute their activity down to the maximum permissible concentrations in drinking water.
29. B. L. Cohen, *Am. Sci.* **64**, 550 (September–October 1976).
30. "High-level nuclear wastes in the seabed," *Oceanus* **20**, 1 (Winter 1977).
31. We thank J. O. Blomeke, H. C. Claiborne, A. M. Weinberg (Oak Ridge National Laboratory), and J. C. Corey (Savannah River Laboratory) for their initial help; also B. Giraud (Service de l'Eau et du Sous-Sol, French Ministry of Industry), J. D. Bredehoeft and I. J. Winograd (U.S. Geological Survey, Reston, Va.), and R. E. Jackson (Environment Canada) for their critical review and comments on an earlier draft of this article.

Bioactivation as a Model for Drug Design Bioreductive Alkylation

Harold W. Moore

The concept of bioactivation as a mechanism of drug action is one that is especially appealing to the medicinal and synthetic organic chemist. The challenge of designing compounds in a biologically inactive form which become activated only subsequent to an in vivo transformation allows the synthesis chemist to take advantage of his arsenal of methodology and mechanistic probes and to directly apply them to potentially important problems of drug action. Most significantly, it permits the making of predictions of the biologically important structural features of a molecule so that they serve as critical guideposts for a synthetic program whose objectives are the construction of biologically active compounds.

A particularly fascinating area within the field of bioactivation is the idea that certain compounds can function as bioreductive alkylating agents (*1*), that is, compounds which become potent alkylating agents after they undergo a reduction in vivo. Such compounds would be expected and several have been shown to possess significant antineoplastic activity (*2–4*). The objectives of this article are to briefly review the field of bioreductive alkylating agents, to point out structural features in a number of natural products which suggest their capability to function as such alkylating agents, and to suggest some specific, but still unknown, compounds that could be predicted to be of potential importance as bioactivated alkylating agents.

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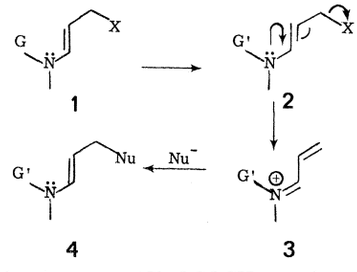
Bioreductive Alkylation

Four simple models can be used to formally catalog potential bioreductive alkylating agents.

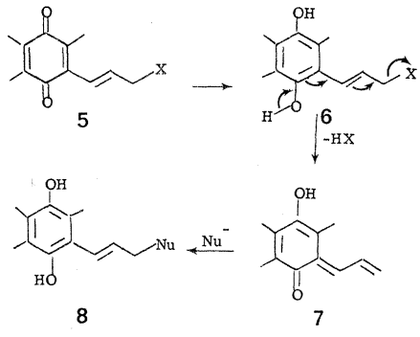
Model 1—activated eneamines. One can envisage a drug of the general formula **1** where X is a leaving group. Such an eneamine, **1**, would undergo facile ionization unless the nonbonding electron pair on nitrogen was sufficiently delocalized into the group G. If this group G (an electron sink) could be converted in vivo to G′, an electron releasing substituent, the drug would become activated and could then function as a potent alkylating agent. This obviously places a severe structural requirement on G. It must be a substituent whose polarity is reversed by an in vivo transformation. Of all the substituents that one can envisage, the electron deficient quinone nucleus is among the more obvious since its reduction in vivo would give an electron rich hydroquinone. Facile ionization would then result in the carbocation **3** which could covalently bond to a biomolecule (such as nucleic acid or protein) resulting in **4**.



X, leaving group (Cl, $OCOCH_3$, tosylate, and the like); Nu, nucleophilic center on a biomolecule (DNA, reductase, or the like); G, electron sink (quinone); and G′, electron releasing group (hydroquinone).

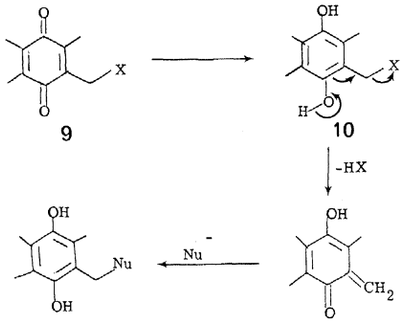
Scheme 1

Model 2—vinylogous quinone methides. Another model that may be important in predicting biological activity is represented in scheme 2. Here it is suggested that alkenyl-substituted quinones, such as **5**, which are functionalized with a leaving group X at the 3 position on the side chain could be reduced in vivo to the hydroquinone **6**. Subsequent loss of HX would give the vinylogous quinone methide **7**, which would then function as a potent alkylating agent via a Michael addition reaction.



Scheme 2

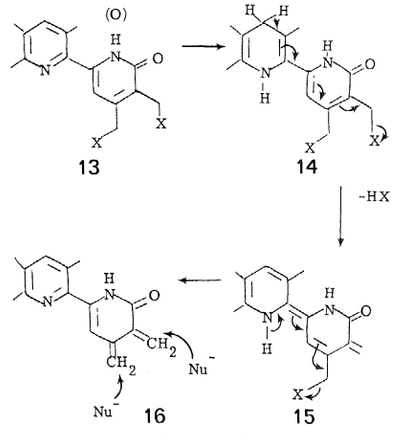
Model 3—simple quinone methides. A third model suggested by Sartorelli, Lin, and co-workers (*1–4*) should be mentioned. They have shown that certain simple quinones which are substituted with one or more $-CH_2$-X substituents show marked antineoplastic activity. On the basis of their results, they have, in fact, proposed that simple quinones such as **9** may function as alkylating agents and suggested that their mode of action is as illustrated in scheme 3, that is, the simple quinone methides **11** are the key alkylating agents in vivo.



Scheme 3

Sartorelli and his co-workers have pointed out that appropriately substituted quinones that are precursors to the quinone methides may allow a therapeutic attack to be effectively directed against the more anaerobic cells of solid tumors (*3*). It has further been observed that the reduced nicotinamide adenine dinucleotide phosphate (NADPH)-dependent enzyme system which reduces naturally occurring quinones such as coenzyme Q and the mitomycins is relatively nonspecific, and thus various structural modifications of the quinone alkylating agents may be accommodated. Finally, the ratio of reduced to oxidized pyridine nucleotide coenzymes may be higher in solid tumors than in normal cells, since in neoplastic cells of solid tumors distal to blood vessels the oxygen tension is decreased. Thus, in such an environment the reduction of substrates by NADPH-dependent enzymes may be enhanced. In fact, Cater and Phillips (*5*) reported a significantly lower oxidation-reduction potential for tumor tissue relative to most normal tissue.

Model 4—α-methylene lactones or lactams. Finally, a fourth model can be envisaged in which the reducible group is a heterocyclic ring, such as a pyridine or quinoline nucleus rather than a quinone (scheme 4). If such compounds are appropriately substituted with CH_2X (X, leaving group) on, for example, a pyrone or α-pyridone nucleus reduction and subsequent eliminations of HX would result in potent alkylating agents. The generalized model represented below illustrates the formation of the potential dialkylating agent **16**, where the alkylating sites are the α-methylene lactam moiety and the double bond in conjugation with the pyridine nucleus. An interesting example of an antineoplastic agent whose mode of action may be cataloged by this model is camptothecin, which will be discussed below.



Scheme 4

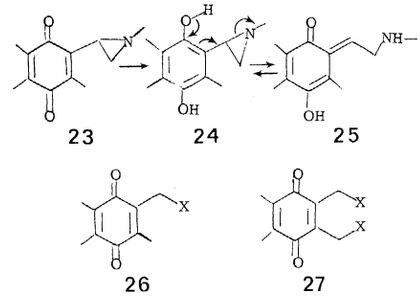
The following are examples of possible bioreductive alkylating agents.

Mitomycin C. An antineoplastic antibiotic, mitomycin C (**17**), has been shown to be an inhibitor of the synthesis of nucleic acids. It is believed to be a dialkylating agent which cross-links DNA, and has been shown to require an initial reduction in order to activate the drug (*6*). Various mechanisms have been proposed (*7*), but the one outlined in scheme 5 is particularly appealing. The salient features of the proposed mechanism of action of this drug are as follows. (i) Mitomycin C is reduced in vivo to the hydroquinone, which then eliminates CH_3OH to give the indole **18**. (ii) The indole could function as an alkylating agent according to model 1 or undergo an elimination process according to model 2. (iii) The driving force for the elimination process would be the release of the steric strain energy of the aziridine ring during the formation of **19**. (iv) Subsequent to the formation of **19**, elimination of HO–$CONH_2$ would give **20**, the proposed biologically active form of mitomycin C. This last step can take place only from **19** and not from the indole **18**; that is, the triggering of this process to give the *bis*-alkylating agent **20** involves the aziridine cleavage step.

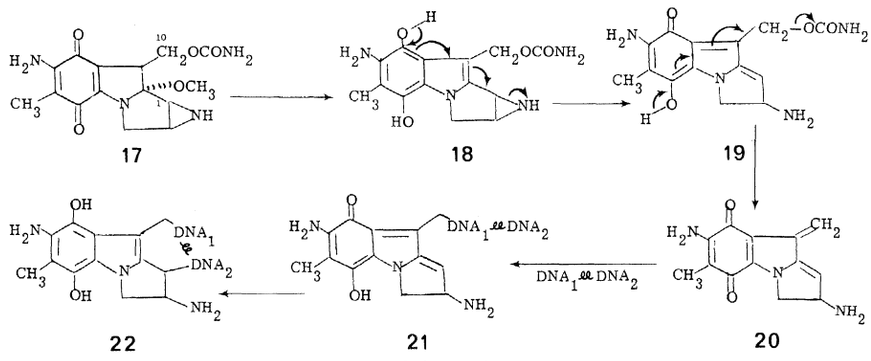
As was mentioned, one of the key steps in the mechanism proposed above is the conversion of **18** to **19**, and this is expected to be facilitated by the release of strain energy of the aziridine ring. Such a process suggests that a series of simple aziridine-substituted quinones (or epoxide-substituted quinones), might be exceedingly powerful bioreductive alkylating agents. Specifically, 2-quinonylaziridines, **23**, should be easily reduced and subsequently undergo ring opening to form simple quinone methides such as **25** (model 3). Depending on the number of aziridine rings substituted onto the quinone nucleus, mono- or polyfunctional alkylating agents could be designed.

To our knowledge, 2-quinonylaziridines such as **23** have not been described. However, Sartorelli and his coworkers (*2–4*) have prepared a number of simple benzo- and naphthoquinones having the general structures **26** and **27** and found that many members of their series function as bioreductive alkylating agents and do show marked antineoplastic activity.

It is also interesting that 1-quinonylaziridines having the general structure **28** have been extensively studied. These compounds were found to be one

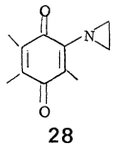


X = $OCOCH_3$, $OCONH_2$, halogen, and so forth.



Scheme 5

of the most active families of quinones in the L1210 system and show additional activity in solid tumor and tissue culture tests (*8*). In fact, one example, **29**, was shown to be highly cytotoxic, and **30** showed the greatest activity of a large number of quinones tested in the L1210 mouse leukemia system as recently reported by the National Cancer Institute (*8*). Compounds in this series are not bioreductive alkylating agents, but rather they function as simple alkylating agents (*9*) that are activated toward nucleophilic attack on the aziridine ring by the presence of the electron-withdrawing quinone nucleus on nitrogen. It is possible that analogous activity and perhaps more selectivity would be observed for the as yet unknown 2-quinoylaziridine series **23** or the corresponding epoxides (or both). Certainly, on the basis of Sartorelli's work, such activity would be anticipated.



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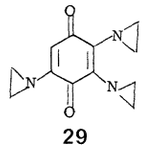

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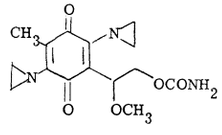

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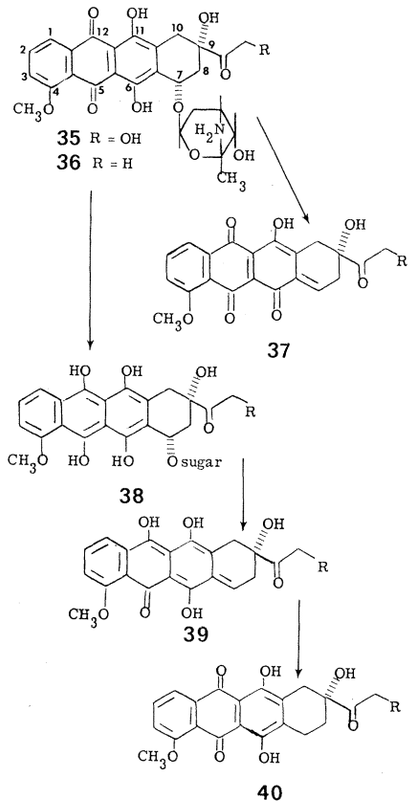
Kinamycin C. Kinamycin C (**31**) has recently been described (*10*) and shown to have marked antibiotic activity. However, it does not yet appear to have been tested for anticancer activity. Such a study would be of interest since there are close structural relationships between this natural product and mitomycin C. Specifically, kinamycin C also is an indole quinone having potential leaving groups ($OCOCH_3$) at positions analogous to positions 1 and 10 of mitomycin C. Thus, it may also function as a bioreductive alkylating agent as outlined in scheme 6 (model 2).

The proposed active forms of kinamycin C and mitomycin C, respectively **34** and **20**, further suggests that simple alkenyl- and dienyl-substituted quinones may function directly as alkylating agents (Michael acceptors) and thus show biological activity.

Anthracyclines and related compounds. Another major class of natural products that show marked anticancer activity are the anthracyclines, adriamycin (**35**) and daunorubicin (**36**). In fact, adriamycin has the widest spectrum of clinical activity of any known compound (*11*). Clinical evaluations have shown it to have significant activity against various tumors including leukemia, lung cancer, breast cancer, sarcoma, lymphoma, and neuroblastoma (*12*). As isolated, adriamycin is a hydroquinone, **35**, which in terms of the bioreductive alkylation concept is the penultimate precursor to the quinone methide. That is, direct elimination of the sugar moiety would give **37** which would function as a reactive Michael acceptor (model 3). A mechanism that is even more in accord with the bioreductive alkylation concept would involve the in vivo reduction of the quinone nucleus in adriamycin to give **38**. Elimination of the sugar group could then proceed as indicated to give the quinone methide **39**. Consistent with this postulate is the fact that reduction of daunorubicin under mild conditions ($Na_2S_2O_4$) results in its quantitative conversion to 7-deoxydaunomycinone **40** (*13*), a tautomer of the quinone methide, **39**. Such a transformation demonstrates that the sugar group at C-7 is exceptionally prone to elimination from the fully reduced natural product. The above views are not intended to imply that adriamycin functions only as an alkylating agent. Indeed, this drug has been shown to intercalate into nucleic acids (*14*). However, conceivably both modes of action may be in operation. Clearly, additional studies of the synthesis and biological activity of adriamycin derivatives having various leaving groups at positions 7 and 10 are warranted.



35 R = OH
36 R = H

37

38

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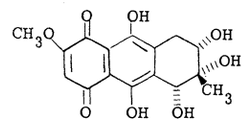

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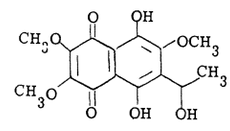

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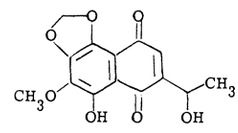

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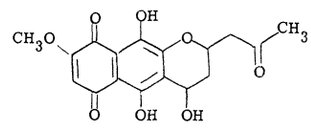

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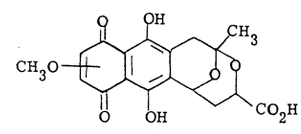

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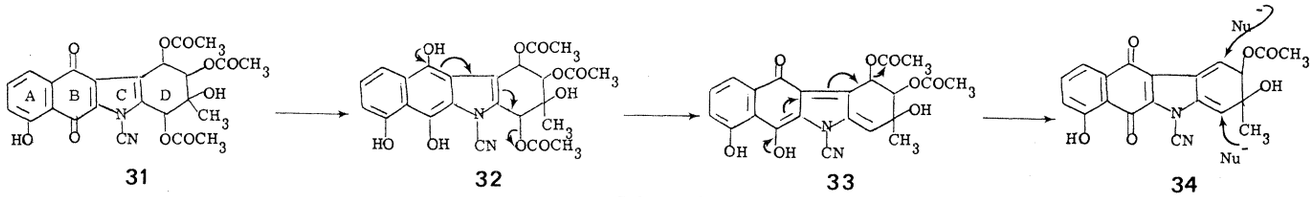
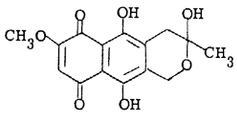
Adriamycin has structural similarities to a number of naturally occurring and biologically active naphthazirins whose mode of action could also be one of bioreductive quinone methide formation. Some selected examples are bostrycin (**41**) (*15*) (antibiotic), lomazarin (**42**) (*16*), lomastilone (**43**) (*16*), erythrostominone (**44**) (*17*) (antibiotic), marticin and isomarticin (**45**) (*18*) (wilting agents found in the plant pathogen, *Fusarium martii*), fu-



31 32 33 34

Scheme 6

sarubin (**46**) (*19*), and a series of anthracyclinone aglycones related to the biologically significant rhodomycinone (*20*, pp. 536–575) series of antibiotics, for example, **47** and **48**. In addition, the antibiotics actinorhodin (*21*), nogalorol (*22*) (the aglycone of the antibiotic, nogalamycin), erythrostominone (*23*), and erythrostominol (*23*) are other examples.



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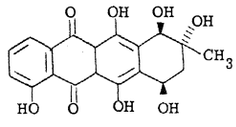

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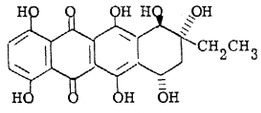

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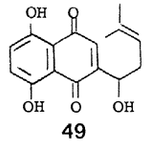

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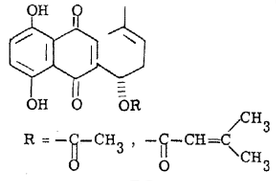

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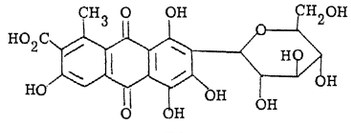

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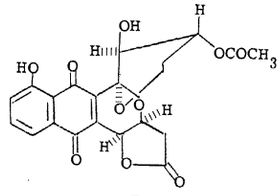
Finally, mention is made of still four additional naphthazirins. Alkannin (**49**) (*S* isomer) and shikonin (**49**) (*R* isomer) have been isolated from boraginaceous roots (*20*, pp. 248–251). From a structural point of view these compounds are suitable to function as bioreductive alkylating agents and thus show cytotoxic properties. In fact, some of the arnebins (**50**), which are alkannin derivatives, have been reported to be active against Walker carcinosarcoma in rats (*24*). A potential problem comes to light here since alkannin is reported to be used for the artificial coloring of certain foods (*25*), and thus, the possible cytotoxic properties of this dye certainly warrant investigation. An analogous situation exists for carminic acid (**51**) (*26*), the coloring principal in cochineal, a dyestuff still employed for coloring certain foods. Cochineal is obtained from the insect *Nopalea coccinellifera* by heat killing the female insects and grinding the bodies to a powder, which contains 10 percent of the pigment carminic acid (**51**). Significantly, the dyestuff, cochineal, has been reported to show anticancer properties (*27*). Intratumoral administration of a cochineal solution containing lactic acid to Jensen rats inhibited the tumor growth in 68 percent of the rats. Also, after intraperitoneal treatment of rats with ascites tumors, 70 percent recovered. However, with Walker tumors no success was observed.

Finally, a number of anthraquinones having a structural similarity to carminic acid should be mentioned, and are described by Thomson (*20*, pp. 536–575). These include tritisporin, asperthecin, isoquinocycline A, avermutin, questinol, fallacinol, carviolin, (*S*)-rhodoptilometrin, averufin, (+)-oxyskyrin, (+)-skyrinol, citreorosein, lucidin, damnacanthol, aloe-emodin, jazunol, and coelulatin. All of these have the 5,10-anthracenedione (anthraquinone) nucleus and a potential leaving group attached to a methylene or methine carbon at position 2. Thus, reductive elimination would again give a reactive Michael acceptor and ultimate alkylation.

Nanaomycin D and related compounds. A number of naturally occurring quinones contain the fused pyrano-γ-lactone moiety such as that found in the antibiotic nanaomycin D (**52**) (*28*). Such a moiety fused to a quinone nucleus results in compounds that would be ideally suited to function as dialkylating agents by the bioreductive mechanism outlined in scheme 7.

Other quinones that contain this heterocyclic moiety and also show antibiotic properties are griseusin A (**57**) (*29*) and γ-naphthocyclinone (**58**) (*30*). Still others are kalafungin (*31*), granaticin (*32*), γ-actinorhodin (*33*), and phenocyclinone (*34*).



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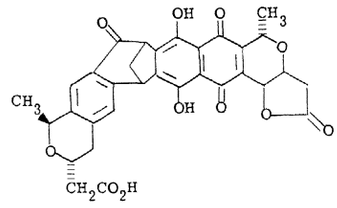

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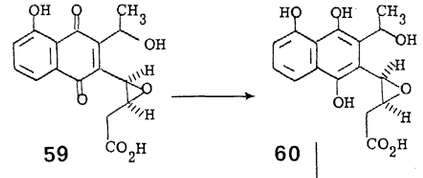
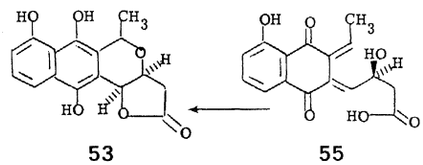
A program directed toward the construction of quinones fused to the pyrano-γ-lactone ring system is called for, and does indeed present a challenge to synthesis chemists. A particularly appealing proposed partial synthesis is outlined below for the construction of nanaomycin (**52**). Specifically, reductive elimination of the epoxide **59** should result in the hydroquinone **53** which would give nanaomycin on oxidation. A special feature of this synthesis is that the penultimate precursor to the hydroquinone **53** is the proposed biologically active bisquinone methide **55**. Thus, the epoxide **59** itself may be biologically active, and structural modifications of this simpler compound are easier to envisage.



59 60



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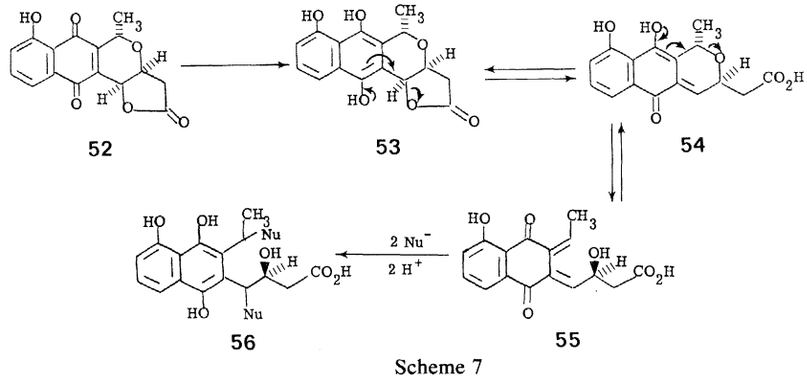
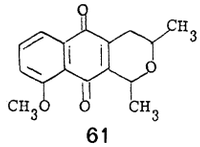
Other quinones of potential importance as bioreductive alkylating agents. An in-depth survey of naturally occurring quinones that are structurally acces-



52 53 54 56 55

Scheme 7

sible to quinone methide formation via a bioreductive mechanism has not been made. However, it does indeed appear that nature has provided a large number of such compounds. Included in such a list are the eleutherins (**61**) (*35*), stemphone (**62**) (fungal pathogen) (*36*), pleurotine (**63**) (antibiotic) (*37*), dehydro-α-lapachone (**64**) (antineoplastic) (*38*), tauranin (**65**) (*39*), altersolanol A (**66**) (plant pathogen) (*40*), hydnuferrugin (**67**) (*41*), cordiachrome G (**68**) (*42*), griseusin B (**69**) (*29*), and conacyton (**70**) (*43*). Other examples are the protoaphins (*20*, pp. 597–628), remerin (*44*), nanaomycin A (*28*), nanaomycin C (*28*), gentisylquinone (*45*), β-methylpyrano-1,4-naphthoquinone (*46*), shanorellin (*47*), α-caryopterone (*48*), and cordiachrome C (*42*).



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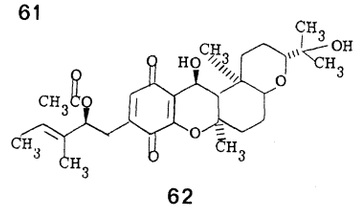

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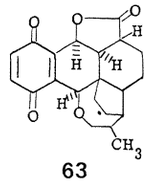

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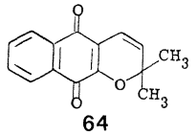

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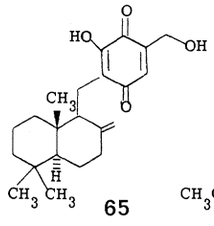

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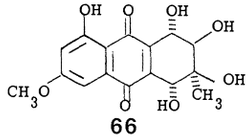

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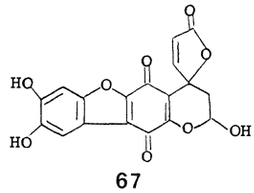

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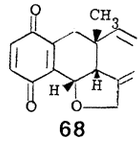

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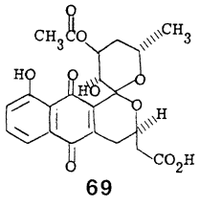

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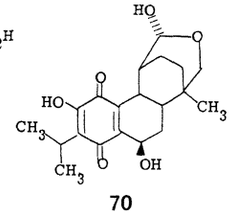
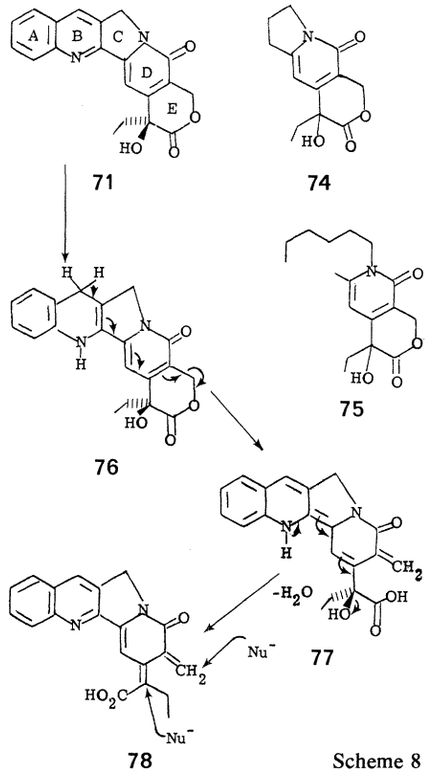


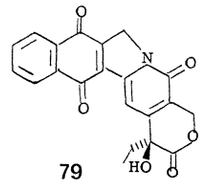
70

Camptothecin and related compounds. Up to this point, the discussion has focused on various quinones as bioreductive alkylating agents. However, this concept need not be limited to this class of compounds. For example, certain alkaloids having the structural features outlined in model 4 may also operate by such a process. The most interesting example is camptothecin (**71**). This alkaloid shows a high activity against several mouse lymphocytic leukemias and also inhibits the growth of certain solid tumors (*49*). Also, 10-hydroxy- and 10-methoxycamptothecin show significant activity against leukemia, L1210. Several attempts have been made to identify the portion of the camptothecin molecule that is responsible for its oncolytic activity. Not only is the α-hydroxylactone portion necessary for antitumor activity, but also the A and B rings appear to be crucial since fragments **74** and **75** have no useful activity (*50*). A mechanism that accounts for this is one of bioreductive alkylation and is outlined in scheme 7. The key features of the mechanism are the initial in vivo reduction of the quinoline nucleus to the dihydro form **76**. Subsequent eliminative ring opening of the lactone nucleus would give **77**. This compound can now lose water to give **78** which has two reactive sites for alkylation, α-methylene lactam and the extended π-system in conjugation with the quinoline ring.



Scheme 8

The proposed mechanism of action of camptothecin as outlined in scheme 8 not only accounts for the reported studies on structure and activity, but it also suggests a large number of related but unknown compounds that may function analogously. For example, replacing the quinoline nucleus by a quinone to give **79** may result in a most potent bioreductive alkylating agent. Also compounds such as **80** and **81** may show activity. In general, compounds of the structural type **82** where G is a reducible group such as a quinone or pyridine derivative and X is a leaving group are the proposed desirable structural features for biological activity.



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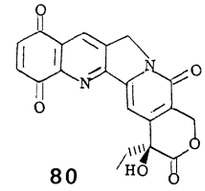

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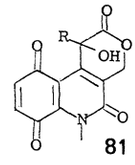

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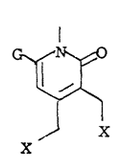
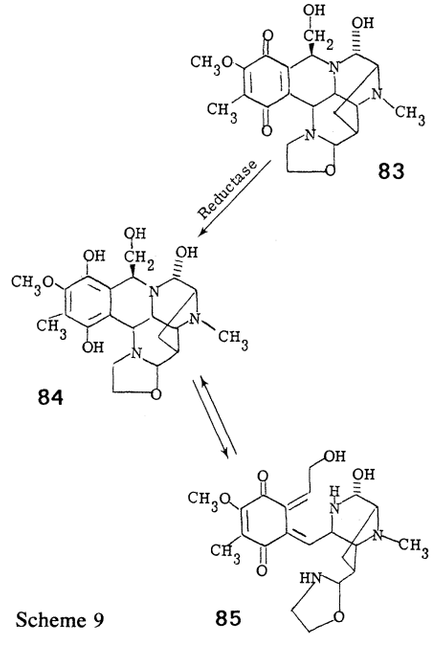


82

Still another alkaloid having structural features suitable to allow it to function as a bioreductive alkylating agent is the antibiotic naphthyridinomycin (*51*) (**83**). Like camptothecin, this compound could also function as a dialkylating agent as outlined in scheme 9.



Scheme 9

A systematic survey of the literature on alkaloids is called for to see whether other compounds are known which are structurally amenable to mechanistic

processes analogous to those outlined in schemes 8 and 9. There are, in fact, an exceedingly large number of alkaloids known which could give quinone methides via an elimination process involving a phenolic hydrogen and the nitrogen of a heterocyclic ring (*52*), that is, analogous to the proposed conversion of **84** to **85**.

Correlation of Bioreductive Alkylation with Biological Data

The National Cancer Institute has recently reported the cancer screening data for 1599 quinones (*8*). Approximately 15 percent of the compounds show activity in one or more of the screens employed, that is, with L1210 leukemia, W-256 system cells, CA-755, S-180, and KB cells. The criteria for minimum activity are normally ≥ 25 percent for L1210 cells; ≥ 58 percent for W-256, CA-755, and S-180 cells; and ≤ 4 μg/ml for KB cells. However, since a large number of compounds in the NCI study were tested at only one dose, the above minimum activity levels were reduced to ≥ 15 percent for L1210; ≥ 45 percent for W-256, CA-755, and S-180; and ≤ 8 μg/ml for the KB test. It is these latter standards that correspond to the 15 percent figure of active compounds mentioned above. If we survey the list of 1599 quinones, we find 97 examples that can be cataloged according to the models for bioreductive alkylation as outlined here. Of these, 48 percent show activity.

Of the 97 compounds cataloged according to the models presented here, 32 are members or derivatives of the mitomycin family (model 1 or 2). Of these, 20 (63 percent) show activity. Another major series which shows marked activity are the anthracyclinones, daunorubicin, adriamycin, and related compounds. Such compounds are cataloged according to model 3, where X, the leaving group, is the sugar moiety. The NCI report includes 20 examples in this series and 12 (60 percent) show activity. The remaining 45 examples are cataloged according to the various model systems, and 15 (33 percent) show significant activity. Finally, it should be mentioned again that Sartorelli and his co-workers (*2–4*) have prepared a large number of benzoquinones, naphthoquinones, quinolinequinones, and naphthazarins that are mono- and disubstituted with CH_2-X (X, leaving group) substituents and have observed that many of these do show antineoplastic activity. That these function as bioreductive alkylating agents and generate reactive quinone methides is further indicated by the fact that no significant activity was observed for these quinones which were not substituted with a leaving group X at the appropriate site.

Summary

The concept of bioreductive alkylation as put forth by Lin, Cosby, Shansky, and Sartorelli (*2*) and further elaborated here is of potential major significance as a mechanism of action of many naturally occurring and synthetic antineoplastic compounds as well as antibiotics. It allows the synthesis chemist to envisage a plethora of compounds that possibly show such activity. In addition, it permits examination of known compounds for the key structural features that may be responsible for their biological activity. Clearly, many possible modes of action other than that of bioreductive alkylation can be envisaged for a number of the compounds discussed in this article. Some of these, in fact, may be more reasonable than the concepts which were outlined. However, it does appear the structural features that are necessary for quinone methide formation, either directly or subsequent to an in vivo reductive process, are ubiquitous. Thus, the possibility of appropriately substituted compounds functioning as bioreductive alkylating agents provides a logical model that has a great deal of predictive power. Finally, although the reactions outlined are not definitive, they suggest the promise of further research in an exceedingly important area of medicinal chemistry.

References and Notes

1. A. J. Lin, L. A. Cosby, A. C. Sartorelli, *Cancer Chemother. Rep.* **4**, 23 (1974).
2. A. J. Lin, L. A. Cosby, C. W. Shansky, A. C. Sartorelli, *J. Med. Chem.* **15**, 1247 (1972).
3. A. J. Lin, R. S. Pardini, L. A. Cosby, B. J. Lillis, C. W. Shansky, A. C. Sartorelli, *ibid.* **16**, 1268 (1973).
4. A. J. Lin, C. W. Shansky, A. C. Sartorelli, *ibid.* **17**, 558 (1974); A. J. Lin, R. S. Pardini, B. J. Lillis, A. C. Sartorelli, *ibid.*, p. 668; A. J. Lin, B. J. Lillis, A. C. Sartorelli, *ibid.* **19**, 917 (1975); A. J. Lin and A. C. Sartorelli, *J. Org. Chem.* **38**, 813 (1973).
5. D. B. Cater and A. F. Phillips, *Nature (London)* **174**, 121 (1954).
6. V. N. Iyer and W. Szybalski, *Science* **145**, 55 (1964); W. Szybalski and V. N. Iyer, in *Antibiotics*, D. Gottlieb and P. D. Shawn, Eds. (Springer-Verlag, New York, 1967), vol. 1, p. 211.
7. M. Tomasz, C. M. Mercado, J. Olson, N. Chatterjie, *Biochemistry* **13**, 4878 (1974).
8. J. S. Driscoll, G. F. Hazard, H. B. Wood, A. Goldin, *Cancer Chemother. Rep.* **4**, 1–362 (1974).
9. H. Nakao and M. Arakawa, *Chem. Pharmacol. Bull.* **20**, 1962 (1972); ———, T. Nakamura, *ibid.*, p. 1968.
10. S. Ōmura, A. Nakagawa, H. Yamada, T. Hata, A Furusaki, T. Watanabe, *ibid.* **21**, 931 (1973).
11. S. Perry, *Cancer Chemother. Rep. Part 1* **51** (1), 17 (1974).
12. For recent representative publications in the medical literature, see among others M. J. Egorin, R. C. Hildebrand, E. F. Cimino, N. R. Bachur, *Cancer Res.* **34**, 2243 (1974); J. A. Gottlieb, J. U. Gatterman, K. B. McCredie, V. Rodrigez, E. Frei III, *ibid.* **33**, 3024 (1973); R. Silverstrini, L. Lenaz, G. DiFronzo, O. Sanfilippo, *ibid.* **32**, 2954 (1973).
13. T. H. Smith, A. N. Fujiwara, D. W. Henry, W. W. Lee, *J. Am. Chem. Soc.* **98**, 1969 (1976).
14. W. J. Pigram, W. Fuller, L. D. Hamilton, *Nature (London) New Biol.* **235**, 17 (1972).
15. T. Noda, T. Take, M. Otani, K. Miyauchi, T. Watanabe, J. Abe, *Tetrahedron Lett.* (1968), p. 6087.
16. R. G. Cooke, J. B. Robinson, J. R. Cannon, R. W. Retallack, *Aust. J. Chem.* **23**, 1029 (1970).
17. B. E. Cross, M. N. Edinberry, W. B. Turner, *Chem. Commun.* (1970), p. 209.
18. A. Pfiffner, thesis, Eidgenössischen Technischen Hochschule, Zurich (1963).
19. G. P. Arsenault, *Can. J. Chem.* **43**, 2433 (1965).
20. R. H. Thomson, *Naturally Occurring Quinones*, (Academic Press, New York, 1971).
21. H. Brockmann, H. Pini, O. V. Plotho, *Chem. Ber.* **83**, 161 (1950).
22. B. K. Bhuyan, R. B. Kelly, R. M. Smith, U.S. patent 3,183,157, cited in *Chem. Abstr.* **63**, 3588 (1965).
23. B. E. Cross, M. N. Edinberry, W. B. Turner, *J. Chem. Soc. Perkin Trans. 1* (1972), p. 380; B. E. Cross and L. J. Zammitt, *ibid.* (1973), p. 2975.
24. S. K. Gupta and I. S. Mathur, *Indian J. Cancer* **9**, 50 (1972); Y. N. Shukla, J. S. Tandon, D. S. Bhakuni, M. M. Dhar, *Phytochemistry* **10**, 1909 (1971).
25. A. C. Jain and S. K. Mathur, *Bull. Natl. Inst. Sci. India 28*, 52 (1965).
26. J. C. Overeem and G. J. M. van der Kerk, *Rec. Trav. Chim. Pays Bas Belg.* **83**, 1023 (1964).
27. N. Mihail and C. Crăciun, *Naturwissenschaften* **57**, 500 (1970).
28. S. Ōmura, H. Tanaka, Y. Okada, H. Marumo, *Chem. Commun.* (1976), p. 320.
29. N. Tsuji, M. Kobayashi, Y. Terui, K. Tori, *Tetrahedron* **32**, 2207 (1976).
30. A. Zeeck and M. Mardin, *Justus Liebigs Ann. Chem.* 7, 1063 (1974); ———, H. Zaehner, *ibid.*, p. 1100.
31. M. E. Bergy, *J. Antibiotics Ser. A* **21**, 454 (1968).
32. S. Barcza, M. Brufani, W. Keller-Schierlein, H. Zähner, *Helv. Chim. Acta* **49**, 1736 (1966).
33. P. Christiansen, thesis, University of Göttingen (1970).
34. H. Brockmann and P. Christiansen, *Chem. Ber.* **103**, 708 (1970).
35. H. Schmid, A. Ebnoëther, Th. M. Meijer, *Helv. Chim. Acta* **33**, 1751 (1950); H. Schmid and A. Ebnöether, *ibid.* **34**, 561 (1951).
36. C. Huber, W. A. Court, J. P. Devlin, O. E. Edwards, *Tetrahedron Lett.* (1974), p. 2545.
37. J. Grandjean and R. Huls, *ibid.*, p. 1893.
38. A. R. Burnett and R. H. Thomson, *J. Chem. Soc. C* (1967), p. 2100.
39. H. Nishikawa, *Proc. Imp. Acad. (Tokyo)* **10**, 414 (1934).
40. A. Stoessl, *Can. J. Chem.* **47**, 767 (1969).
41. J. Gripenberg, *Tetrahedron Lett.* (1974), p. 619.
42. M. Moir and R. H. Thomson, *J. Chem. Soc. Perkin Trans. 1* (1973), p. 1556.
43. W. H. Watson and Z. Taira, *Tetrahedron Lett.* (1976), p. 2501.
44. R. D. Allan, R. J. Wells, J. K. MacLeod, *ibid.* (1973), p. 7.
45. B. G. Engel and W. Brzeski, *Helv. Chim. Acta* **30**, 1472 (1947).
46. W. Sandermann, M. H. Simatupang, W. Wendeborn, *Naturwissenschaften* **55**, 38 (1968).
47. C. K. Wat, A. Tse, R. J. Bandoni, G. H. N. Towers, *Phytochemistry* 7, 2177 (1968).
48. T. Matsumoto, C. Mayer, Ch. H. Eugster, *Helv. Chim. Acta* **52**, 808 (1969).
49. M. Shamma and V. St. Georgiev, *J. Pharmacol. Soc.* **63**, 163 (1974); A. G. Schultz, *Chem. Rev.* **73**, 385 (1973). See also R. E. Lyle, J. A. Bristol, M. J. Kane and D. E. Portlock [*J. Org. Chem.* **38**, 3268 (1973)] and the references cited therein.
50. M. C. Wani and M. E. Wall, *J. Org. Chem.* **34**, 1364 (1969); M. Shamma, *Experientia* **24**, 107 (1968).
51. J. Sygusch, F. Brisse, S. Hanessian, *Tetrahedron Lett.* (1974), p. 4021; *ibid.*, No. 3 (1975), errata.
52. J. S. Glasby, *Encyclopedia of the Alkaloids* (Plenum, New York, 1975), vols. 1 and 2.
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