Structure–Activity Relationship Study of Anthraquinones: 1,4-Dihydroxy-5,8-bis[[2-(2-hydroxyethoxy)ethyl]amino]-9,10-anthracenedione, an Analog of an Established Antineoplastic Agent

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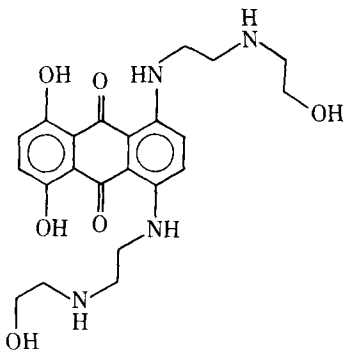
Abstract □ An oxygen analog of the antineoplastic anthraquinone, 1,4-dihydroxy-5,8-bis[[2-(2-hydroxyethyl)amino]ethyl]amino - 9,10 -anthracenedione, was synthesized. This compound, 1,4-dihydroxy-5,8-bis[[2-(2-hydroxyethoxy)ethyl]amino]-9,10-anthracenedione, was found to be inactive against P-388 lymphocytic leukemia. A comparative structure–activity study of these two anthraquinones in terms of previously postulated N—O—O triangulation hypothesis was discussed.

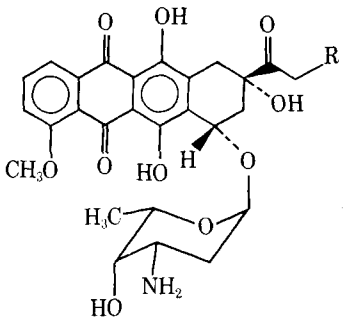
Keyphrases □ Antineoplastic agents—structure–activity relationship, 5,8-bis[[2-(2-hydroxyethoxy)ethyl]amino]-9,10-anthracenedione □ Structure–activity relationships—5,8-bis[[2-(2-hydroxyethoxy)ethyl]-amino]-9,10-anthracenedione □ Anthraquinones—antineoplastic agents, 5,8-bis[[2-(2-hydroxyethoxy)ethyl]amino] - 9,10-anthracenedione, structure–activity relationships

The importance of the nitrogen atom in the center of the side chain of 1,4-dihydroxy-5,8-bis[[2-(2-hydroxyethyl)-amino]ethyl]amino-9,10-anthracenedione (I), an outstanding antineoplastic drug, was noted previously (1, 2). Replacement of this critical nitrogen atom by other atoms, such as sulfur or carbon, resulted in compounds with no inhibitory action against leukemias P-388 or L-1210 in experimental animals (1). Based on the proposed N—O—O triangulation hypothesis (3), the structural and spatial relationship of this nitrogen atom to two oxygen atoms on the dihydroxyanthracenedione ring (I) has been correlated with that of the amino atom of daunosamine to the two oxygen functions on the aglycones of daunorubicin (II*a*) and doxorubicin (II*b*) (4, 5). The reported biological activity profile of these aminoanthraquinones and anthracycline antibiotics also has been found to be similar (5–7).

Interestingly, in recent publications, certain analogs of the anthracycline antibiotics, with the amino function of

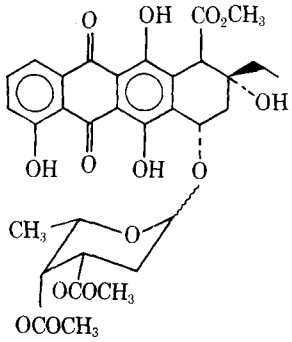


I

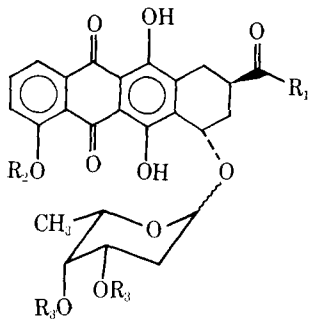


II*a*: R = H
II*b*: R = OH

the amino sugar moiety replaced by a hydroxyl or an acetoxyl group, possessed activity against P-388 or L-1210 leukemia.



III



IV*a*: R_1 = H, R_2 = CH_3, R_3 = H
IV*b*: R_1 = H, R_2 = CH_3, R_3 = $COCH_3$
IV*c*: R_1 = OH, R_2 = CH_3, R_3 = H
IV*d*: R_1 = OH, R_2 = CH_3, R_3 = $COCH_3$
IV*e*: R_1 = H, R_2 = H, R_3 = H

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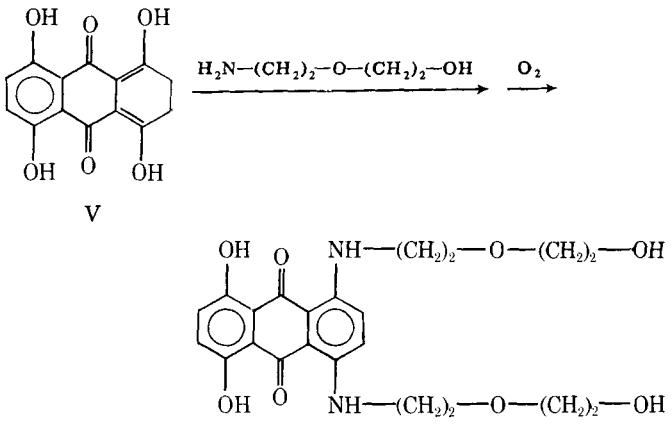
These compounds include 2′-deoxy-di-*O*-acetyl-D-ribopyranosyl-ϵ-rhodomycinone (III) (8), 7-*O*-(2,6-dideoxy-α-L-*lyxo*-hexopyranosyl)daunomycinone (IV*a*), 3′-deamino-3′-hydroxydaunorubicin) and its diacetyl derivative (IV*b*) (9), the corresponding 3′-deamino-3′-hydroxydoxorubicin analog (IV*c*) and its diacetyl derivative (IV*d*) (10), and 2′-deoxy-L-fucopyranosylcarminomycinone (IV*e*) (11). However, the dosages required for activity are generally larger than those for the established antineoplastic agents I, II*a*, and II*b*. Activity displayed by these oxygenated analogs may not always be as potent. In addition, most other glycosides synthesized by these investigators failed to show activity against P-388 or L-1210 leukemia (8–11). Nevertheless, the information suggests that the significance of the nitrogen atom of compound I should be reexamined with respect to the corresponding oxygen atom. Consequently, 1,4-dihydroxy-5,8-bis[[2-(2-hydroxyethoxy)ethyl]amino] - 9,10-anthracenedione (VI) was synthesized.

EXPERIMENTAL

Compound VI was synthesized by placing 2.75 g (0.01 mole) of purified 5,8-dihydroxyleukoquinizarin (V) in a round-bottom flask equipped with a mechanical stirrer and a condenser. To this, 10.5 g (0.1 mole) of 2-(2-aminoethoxy)ethanol was added dropwise, with stirring. The mixture was heated with stirring under nitrogen at 60° in an oil bath for 2 hr, and allowed to stand at room temperature overnight. On the next day, the stirring rod (rinsed with 100 ml of ethanol which was added into the reaction mixture) was replaced by a glass sparge tube. Dry air was bubbled through the tube into the warm (50–60°) mixture for 4 hr, during which time the top of the condenser was connected to a water aspirator so that the entire system was under a slightly reduced pressure. The mixture was chilled and the separated solid product collected by filtration, washed successively with ethanol (10 ml), petroleum ether (20 ml), and diethyl ether (2 × 20 ml), and dried to give 3.66 g (82% yield) of VI. Recrystallization from a mixture of ethanol and petroleum ether (2:1) gave analytically pure VI as dark blue crystals, mp 156–157° (Scheme I). UV: λ_{max} (ethanol) 190 (log ϵ 4.23), 214 (4.35), 232 (4.48), 270 (4.07), 380 (3.69), 512 (3.52), 563 (3.86), 610 (4.31), and 662 (4.34) nm.

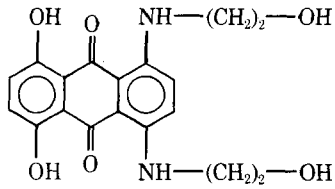


Scheme I

Anal.—Calc. for $C_{22}H_{26}N_2O_8$: C, 59.18; H, 5.87; N, 6.28. Found: C, 59.27; H, 6.03; N, 6.39.

RESULTS AND DISCUSSION

Although compound I has shown consistently outstanding antineoplastic activity in a number of experimental animal systems (1, 2, 5), compound VI was inactive against P-388 leukemia in the National Cancer Institute screening (T/C values at 200, 100, 50, and 25 mg/kg were 113, 110, 103, and 102%, respectively)[1]. This information, and the earlier negative test results of 1,4-dihydroxy-5,8-bis[(2-hydroxyethyl)amino]-9,10-anthracenedione (VII) against L-1210 leukemia (T/C values at 400, 200, and 100 mg/kg were 113, 110, and 103%, respectively), indicated that the oxygen atom (either in the form of —OH or —OR) cannot replace the particular nitrogen atom for antineoplastic activity in the aminoanthraquinone series.



VII

The relevancy of this nitrogen atom to the originally proposed N—O—O triangulation pharmacophore (3) is also reaffirmed.

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[1] For the general screening procedure, see Ref. 12. For the test data interpretation, see Instruction Booklet 14, "Screening Data Summary Interpretation and Outline of Current Screen," Drug Evaluation Branch, Division of Cancer Treatment, National Cancer Institute, Bethesda, MD 20014. In general, a minimum increase in survival of treated animals over controls resulting in a T/C ≥ 125% is necessary for a compound to be considered as active.