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Syntheses of Morindaparvin A and Its Derivatives

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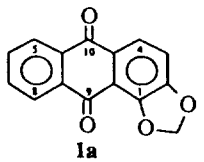
A general route for convergent syntheses of morindaparvin derivatives with 1,2-methylene-dioxyanthraquinone pattern is described. The anion of 2-methoxycyclohexanone (**3**), generated with lithium cyclohexylisopropylamine at −78℃, was sulfenylated with phenyl phenylthiosulfonate followed by elimination to afford α, β-unsaturated carbonyl system **8**. 6-Methoxy-2-cyclohexen-1-one (**8**) was condensed with the four phthalide sulfones derivatives **10a-d**, to provide morindaparvin derivatives, **1a-d**.

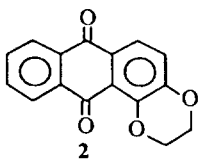
Introduction

The rhizome and root of *Morinda Parvifolia* Bartl. (Rubiaceae) are well known as medicinal plants in Chinese folklore, and are used as herbal remedies for the treatment of bronchitis and whooping cough in humans.[1] From this plant, Chang and others have isolated and determined the structure of morindaparvin A & B which exhibit good biological activities[2] including antitumor activities. A number of morindaparvin analogs[3] with different substituents on the phenyl rings and its derivatives possessing an ethylenedioxy group at 1 to 4 position have been synthesized. Also, many other researchers[2,3] have discovered that morindaparvin contains potential antitumor properties. Based on this finding, it has been reported that not only morindaparvin with various kinds of substituents but also their derivatives[2,4] similar to **2**, containing ethylenedioxy group at the positions 1 and 2, have been synthesized.



1a

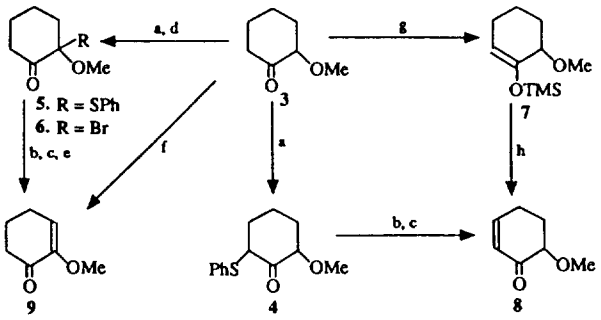
Morindaparvin A



2

1,2-Ethylenedioxyanthraquinone (or 1,2-Methylenedioxyanthraquinone)

However, any derivatives with a hydroxyl group at either 5 or 8 position have not been synthesized. The hydroxyl group at either position will form an intramolecular hydrogen bonding with a carbonyl group in the quinone moiety, and consequently it may alter biological activity. To this end, we synthesized four morindaparvin derivatives **1a-d** and would like to report the synthesis of theses compounds in this paper.



Scheme 1. (a) See the Table 1; (b) $NaIO_4$ (1.1 eq)/MeOH : H_2O=5 : 3, 0℃, rt, 24 h, 92%; (c) $CaCO_3$ (1.5 eq)/benzene, rfl, 12 h, 84%; (d) LDA (1.1 eq)/THF, −78℃ (0.5 h), Br_2(1.0 eq)/CH_2Cl_2, rt, 0.5 h, 61%; (e) DBU (1.3 eq)/benzene, rfl, 12 h, 23%; (f) Method A: DDQ (2.0 eq)/dioxane, rfl, 32 h, 33%; Method B: DDQ (2.0 eq)/benzene, rfl, 32 h, 16%; (g) Method A: LDA (1.1 eq)/THF, TMSCl (1.7 eq), −78℃ (1 h), 25℃ (1 h), 51%; Method B: LDA (1.1 eq)/DME, TMSCl (1.7 eq), 0℃ (20 min), 25℃ (15 min), 21%; (h) DDQ/collidine (1.5 eq)/benzene, rt, 18 h, 48%.

Results and Discussion

The principal reaction for the synthesis of 1 is the Michael type reaction between phthalide sulfone 10[5] and enone **8**. The precursor **4** of Michael acceptor component **8** was prepared from 2-methoxycyclohexanone (**3**)[6] as shown in Scheme 1.

There are numerous literature[7] precedents in which the double bond is generated on the same or the opposite side of the methyl substituent when 2-methylcyclohexanone is converted to its corresponding enone system. However, in the case of other substituents, there are very few examples known in the literature. One known example[8] is the formation of 6-hydroxy-2-cyclohexen-1-one from 2-cyclohexen-1-one via silyl enol ether. Trost[9a] reported that, in the case of 2-methylcyclohexanone, there is no difference in the ratio of two regioisomers between when the enolate generated in kinetically controlled conditions at −78℃ was added to $PhSO_2SPh$ and when the electrophile was added to the enolate. On the other hand, in the case of 2-methoxycyclohexanone (**3**), the former conditions provided **5** as a major product and the latter conditions gave **4** as a major product. Therefore, we have examined the reaction conditions[9] to find the conditions which would provide **4** predominantly, as shown in Table 1. When the enolate is generated at −78℃ and $PhSO_2SPh$[10] is used as an electrophile (entry 2, 6), the compound **4** was generated in a regioselective manner. The stereochemical relationship between two substituents, SPh & OMe, was proved to be all equational form as determined by NOESY and COSY techniques.

In order to explain regioselectivity of two enolates, the heat of formation and net charge of four enolates were calculated by AM1 method (Table 2). Since the difference in the net charge between the enolate of entry 1 and 2 is greater than that of between the enolate of entry 3 and 4, it was expected that there would be a significant difference in the regioselectivity, if the net charge of the enolates is an important factor in determining the reaction rate of two enolates. However, experimental result in the sulfenylation showed that the there was no significant difference in the ratio of two regioisomers formed, indicating that there would be other factors controlling the regioselectivity. The regioselectivity with $PhSO_2SPh$ as an electrophile was better than with PhSSPh and the purification procedure was much easier.

As an alternative way of preparing **8** from **3**, the compound **3** was treated with DDQ in benzene or dioxane solution.[11] Under this conditions, the compound **8** was not obtained but instead the compound **9** was obtained only in 16-33% yield. Alternatively, when **3** was brominated first and the resulting bromo compound was treated with DBU,[12] only the compound **9** was formed in 23%. However, when **3** was converted initially to silyl enol[13] (LDA/TMS-Cl) and then the resulting enol ether was terated with DDQ, **8** was obtained in 48% yield (in the case of 6-methyl-2-cyclohexen-1-one, the yield is 73%).

Among all of the examined conditions, in the case of 2-methoxycyclohexenone **3**, the sulfenylation (LiCIPA, $PhSO_2$ SPh) followed by elimination[9,14] was found to be the best way for the preparation of 6-methoxy-2-cyclohexen-1-one (**8**).

Thus prepared **8** reacted[5] with phthalide sulfone **10** to give **11** which was then oxidized[5b] by bubbling O_2 into the reaction mixture to give the anthraquinone derivatives **12**. The demethylation[15] by BBr_3/dimethylsulfide and alkylation[16] with dichloromethane provided new morindaparvin derivatives **1a-d**.

Experimental

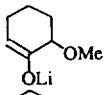
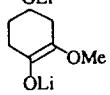
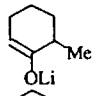
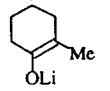
All reactions were performed under N_2 or Ar gas. All rea-

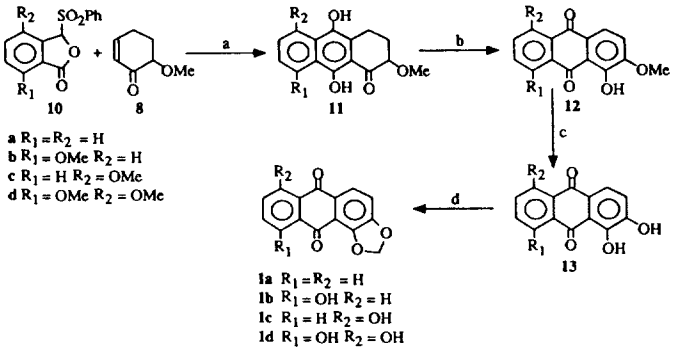
Table 1. Sulfenylation of **3** by PhSSPh and $PhSO_2SPh$ under Various Basic Conditions

Run	Reaction condition	Electrophile	Ratio (**4**/**5**)[a]	Product (% yield)[b]
1.	LDA (1.1 eq.)/THF −78℃ (1 hr), 25℃ (1.5 hr)	PhSSPh	5/1 (4/1)	85% (87%)
2.	〃	$PhSO_2SPh$	95/1	84%
3.	LDA (1.05 eq.)/DME −20℃ (25 min), 30℃ (35 min)	PhSSPh	2.7/1	76%
4.	〃	$PhSO_2SPh$	2.6/1	50%
5.	LiCIPA (1.1 eq.)/THF −78℃ (10 min), 25℃ (20 min)	PhSSPh	11/1	64%
6.	〃	$PhSO_2SPh$	95/1 (97/3)	94% (85%)
7.	LiCIPA (1.1 eq.)/DME −20℃ (25 min), 30℃ (35 min)	PhSSPh	2.7/1	69%
8.	〃	$PhSO_2Ph$	6.1/1	57%

[a]Determined by GC. [b]Yield of isolated product. [c]Parentheses indicate the yields of sulfenylation for 2-methylcyclohexanone.[9a]

Table 2. Heat of Formation and Net Charge for Each Lithium Enolates

Entry	Anion	Heat of formation (Kcal)	Net charge	
1		−100.6977	−0.6085	}0.1809
2		−105.4573	−0.4276	
3		−67.7124	−0.5863	}0.0501
4		−72.8141	−0.5362	



Scheme 2. *t*-BuOLi (2.5 eq)/THF, −78℃, **8** (0.92 eq)/THF, rt (1 h), rfl (0.5 h), 87%; (b) O_2/DMF, rfl, 6 h, 86%; (c) BBr_3SMe_2 (4.0 eq)/1,2-dichloroethane, rfl, 24 h, 78%; (d) CsF (5.0 eq), CH_2Cl_2 (1.1 eq)/DMF, 2 hr, rfl, 2 h, 89%.

gents and solvents were dried and purified according to the conventional procedures immediately before use. Melting points were determined using Buchi 510 apparatus and are uncorrected. IR spectra were taken in KBr on a Nicolet 5-DXB grating spectrophotometer. UV spectra were recorded on a Beckmann DB-8B spectrophotometer. ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) spectra were taken on a JEOL JMN-EX 400 spectrometer. NMR spectra were run in $CDCl_3$ solution and chemical shifts were related to TMS. GC/MS spectra were obtained on a Nermag Model R10-10C spectrometer and the data reported are the m/z values for the most abundant peaks. E. Merck silica gel 9385(230-400 mesh) was used for flash chromatography.

2-Methoxy-6-phenylthiocyclohexanone (4). To a stirred solution of LiCIPA at −78℃, prepared from *N*-isopropylcyclohexylamine (1.41 mL, 8.58 mmol) and *n*-BuLi (5.84 mL, 1.47 M, 8.58 mmol) in THF (10 mL) was added a solution of methoxy compound **3** (1.0 g, 7.80 mmol) in THF (10 mL) dropwise by syringe. After complete addition, the reaction was kept at −78℃ for 1 h. Phenyl phenylthiosulfonate (2.34 g, 9.36 mmol) in 5 m*l* of THF was added immediately to a cold enolate solution, then allowed to warm to 25℃ for 20 min. The mixture was poured into a combined solution (ether/1 N HCl=3 : 1). The layers were separated and organic layer washed successively with 1 N HCl, saturated $NaHCO_3$, and then dried ($MgSO_4$), filtered and evaporated at reduced pressure. The residue was purified by distillation, and then flash chromatography (EtOAc/hexane=3 : 2) to afford **4** as a colorless oil; yield: 1.70 g (94%); bp. 187℃/17 torr; ^{1}H-NMR ($CDCl_3$/TMS): δ 7.45 (m, 2H, Ar), 7.29 (m, 3H, Ar), 3.87 (dd, 1H, J=11.17, 5.20 Hz, CH_a-OMe), 3.84 (dd, 1H, J=12.34, 5.97 Hz, CH_a-SPh), 3.46 (s, 3H, OMe), 2.32 (m, 2H), 1.94 (m, 1H), 1.68 (m, 3H); ^{13}C-NMR ($CDCl_3$/TMS): δ 204.43, 133.32, 132.80, 128.93, 128.89, 128.85, 127.44, 84.48, 58.03, 57.25, 35.66, 34.50, 22.87. IR (KBr): ν=2938, 1721, 779; MS: m/z=236 (M^+, 7%), 127 (78), 98 (100), 67 (74). **5**: ^{1}H-NMR ($CDCl_3$/TMS): δ 7.39 (m, 2H, Ar), 7.28 (m, 3H, Ar), 3.52 (s, 3H, OMe), 2.89 (m, 1H), 2.40 (m, 1H), 2.27 (m, 1H), **7**: ^{1}H-NMR ($CDCl_3$/TMS): δ 4.94 (t, 1H, J=4.1 Hz, =CH), 3.39 (s, 3H, OMe), 2.17-0.89 (m, 7H), 0.17 (s, 9H, OTMS).

6-Methoxy-2-cyclohexen-1-one (8). Phenylthio compound **4** (1.38 g, 5.84 mmol) was dissolved in 20 mL of methanol and cooled in an ice bath prior to the dropwise addition of a solution of $NaIO_4$ (1.37 g, 6.42 mmol) in water (12 mL). After complete addition, the ice bath was removed, and

Table 3. Morindaparvin A derivatives **1a-d** prepared

Product	mp(℃)	IR (KBr) ν cm^{-1}	^{1}H-NMR ($CDCl_3$/TMS), δ, J (Hz)	UV (MeOH) λ_{max} (nm), log ε	MS (70 eV) m/z (%)
1a	283-285	2924, 1665, 1581, 1489, 1454, 1293, 1257, 1025, 990, 927, 842, 716	8.15 (m, 2H, Ar), 7.83 (d, 1H, J=8.7, Ar), 7.67 (m, 2H, Ar), 7.04 (d, 1H, J=7.9, Ar) 6.20 (s, 2H, CH_2).	259.2 (2.20) 237.9 (1.70) 214.2 (1.25)	252 (M^+, 88), 223, 196, 163 (100)
1b	276-278	3444, 2924, 1672, 1588, 1496, 1454, 1293, 1257 1032, 990, 927, 835 716	13.68 (s, 1H, OH), 8.30 (m, 2H, Ar), 7.98 (d, 1H, J=7.9, Ar), 7.78 (d, 1H, J=8.5, Ar), 7.14 (d, 1H, J=7.9, Ar), 6.32 (s, 2H, CH_2).	259.6 (1.47) 238.8 (1.02) 213.8 (0.74)	268 (M^+, 5) 251(100) 138 (33)
1c	177-179	3446, 2924,1735, 1602, 1454, 1377, 1290, 1243, 1032, 913, 807, 730	12.81 (s, 1H, OH), 8.00 (d, 1H, J=8.7, Ar), 7.71 (m, 2H, Ar), 7.53 (d, 1H, J=8.7, Ar), 7.15 (d, 1H, J=7.9, Ar), 6.33 (s, 2H, CH_2).	237.9 (1.51) 215.4 (1.34)	simillar to **1b**
1d	270-272	3437, 2924, 1630, 1581, 1461, 1257, 1222, 1032, 920, 786	13.06 (s, 1H, OH), 12.84 (s, 1H, OH), 8.02 (d, 1H, J=8.4, Ar), 7.27 (d, 2H, J=7.9, Ar), 7.18 (d, 1H, J=8.4, Ar), 6.42 (s, 2H, CH_2).	243.8 (0.64) 214.2 (0.24)	284 (M^+, 100) 268 (49)

the reaction was stirred at room temperature for 24 h. The reaction mixture was filtered, and the precipitate was washed several times with MeOH, then worked up as usual method. The residue was purified by chromatotron (10% EtOAc in CH_2Cl_2) to afford the desired 2-methoxy-6-phenylsulfinylcyclohexanone as a colorless oil; yield: 1.35 g (92%); ^{1}H-NMR ($CDCl_3$/TMS): δ 8.07 (m, 2H, Ar), 7.56 (m, 3H, Ar), 3.56-4.06 (m, 2H, 2×CH), 3.38 (s, 3H, OMe), 1.49-2.63 (m, 6H). A vigorously stirred mixture of 2-methoxy-6-phenylsulfinylcyclohexanone (2.0 g, 7.93 mmol), $CaCO_3$ (1.19 g, 11.89 mmol) and dried benzene (50 mL) was heated at reflux for 12 h. The reaction was cooled and then filtered to remove inorganic material. The solvent was evaporated and the residue dissolved in ether (50 mL). The mixture was washed successively with brine, water, then dried ($MgSO_4$), filtered and evaporated at reduced pressure. The residue was purified by column chromatography and chromatotron (EtOAc/hexane=3 : 2) to afford **8** as a colorless oil; yield: 0.84 g (84%); bp. 72-74℃/2.15 torr, ^{1}H-NMR ($CDCl_3$/TMS): δ 6.83 (dt, 1H, J=10.0, 4.1 Hz, =CH), 5.90 (dt, 1H, J=10.0, 1.8 Hz, =CH), 3.69 (dd, 1H, J=10.34, 4.6 Hz, CH), 3.41 (s, 3H, OMe), 2.51-1.86 (m, 4H); MS: m/z 126 (M^+, 98%), 95 (37), 55 (100). **9**: ^{1}H-NMR ($CDCl_3$/TMS): δ 5.80 (t, 1H, J=4.4 Hz, =CH), 3.53 (s, 3H, OMe), 2.51-2.29 (m, 2H), 2.08-1.84 (m, 2H), 1.25-1.11 (m, 2H).

A typical experimental procedures from **11** to **1** are as follows:

5,10-Dihydroxy-4,7-dimethoxy-7,8,9-trihydro-6-naphthacene (11b). To a cold (−78℃) stirred solution of lithium *t*-butoxide, prepared from *t*-butyl alcohol (0.95 mL, 10.07 mmol) and *n*-BuLi (6.63 mL of 1.47 M solution, 9.75 mmol) in dry THF (15 mL) under N_2 was added the sulfone **10b** (1.09 g, 3.57 mmol) as a slurry in THF (15 mL). Upon complete addition of the sulfone, the orange-yellow mixture of partially precipitated anion was stirred for 20 min at −78℃. A solution of the cyclohexenone **8** (0.41 g, 3.25 mmol) in THF (5 mL) was added by syringe, and the mixture was stirred at −78℃ for 1 h. The cooling bath was removed, and the reaction was allowed to warm to room temperature and then refluxed for 30 min, during which time an orange-red precipitate formed. The reaction mixture was cooled at 0℃ and acidified with 2 N HCl. The THF was evaporated under reduced pressure, and the aqueous mixture was extracted with EtOAc (3×50 mL). The combined EtOAc extracts were washed successively with saturated $NaHCO_3$, 3% $NaHSO_3$, H_2O and brine, dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Trituration of the syrupy residue with Et_2O gave a crude compound **11b**.

5-Hydroxy-4,6-dimethoxyanthraquinone (12b). Oxygen was bubbled through a heated (110℃) solution of the crude **11b** (0.94 g, 3.26 mmol) in DMF (60 mL) for 6 h. The oxygen flow was terminated, and the solution was cooled in an ice-water bath. Addition of H_2O (20 mL) to the solution precipitated **12b** as yellow solid, which was collected by filtration, washed with H_2O, and dried to give pure **12b**; yield: 0.8 (86%); mp. 218-220℃; ^{1}H-NMR ($CDCl_3$/TMS): δ 13.12 (s, 1H, OH), 8.32 (m, 2H, Ar), 7.89 (d, 1H, J=7.8 Hz, Ar), 7.81 (m, 1H, Ar), 7.19 (d, 1H, J=8.8 Hz, Ar), 4.03, 4.01 (3H, each, s, OMe), **12a**: ^{1}H-NMR ($CDCl_3$/TMS): δ 13.57 (s, 1H, OH), 8.11 (m, 2H, Ar), 7.80 (d, 1H, J=8.7 Hz, Ar), 7.65 (m, 2H, Ar), 7.02 (d, 1H, J=7.9 Hz, Ar), 4.01 (s, 3H, OMe). **12c**: mp. 165-167℃; ^{1}H-NMR ($CDCl_3$/TMS): δ 12.84 (s, 1H, OH), 7.97 (d, 1H, J=7.7 Hz, Ar), 7.81 (dd, 1H, J=8.4, 0.7 Hz, Ar), 7.71 (t, 1H, J=8.1 Hz, Ar), 7.36 (d, 1H, J=8.4 Hz, Ar), 7.17 (d, 1H, J=8.8 Hz, Ar), 4.04, 4.00 (3H each, s, OMe). **12d**: ^{1}H-NMR ($CDCl_3$/TMS): δ 13.08 (s, 1H, OH), 8.04 (d, 1H, J=8.1 Hz, Ar), 7.31 (d, 2H, J=8.1 Hz, Ar), 7.20 (d, 1H, J=8.4 Hz, Ar), 4.12, 4.07, 4.03 (3H each, s, OMe).

4,5,6-Trihydroxyanthraquinone (13b). To a flame-dried flask under N_2 was added boron tribromide/dimethyl sulfide (0.89 mL, 0.89 mmol) in 10 mL of 1,2-dichloroethane. To this solution was transfered **12b** (63 mg, 0.22 mmol) in 10 mL of 1,2-dichloroethane by means of a cannula using N_2 pressure. The reaction was stirred at reflux for 24 h. The mixture was hydrolyzed by adding 20 mL of H_2O, stirring for 20 min and diluting with CH_2Cl_2. The organic layer was separated and washed with 1 M $NaHCO_3$ and the solution was subsequently taken up with 1 N NaOH (3×20 mL). The combined NaOH washings were acidified and the product was subsequently extracted into CH_2Cl_2, dried ($MgSO_4$) and the solvent removed. The yellow residue was purified by column chromatography to afford **13b** as a red crystals; yield: 44.5 mg (78%). **13a, 13b, 13c** and **13d** are insoluble in most common organic solvents.

5-Hydroxy-1,2-methylenedioxyanthraquinone (1b). To a stirred solution of **13b** (28 mg, 0.11 mmol) in dried DMF (10 mL) was added CsF (83 mg, 0.55 mmol) and CH_2Cl_2 (8 mL, 0.12 mmol), and the solution was heated under reflux for 2 h. The reaction mixture was diluted with CH_2Cl_2 and washed successively with H_2O and brine. The organic layer was dried and concentrated under reduced pressure. The residue was purified by column chromatography (10% EtOAc in CH_2Cl_2) to afford **1b** as a yellow crystals; yield: 26 mg (89%).

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Cu^{2+}-Anthraquinone Complexes: Formation, Interaction with DNA, and Biological Activity

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Growth inhibition potency of the anthraquinones, anthraquinone-1,5-disulfonic acid and carminic acid, for Sarcoma 180 and L1210 leukemia cells *in vivo* and *in vitro*, was induced by the divalent transition metal ion, Cu^{2+}. On the other hand spectroscopic titration data show that the anthraquinone drugs form Cu^{2+} chelate complexes (carminic acid : Cu^{2+} = 1 : 6; anthraquinone-1,5-disulfonic acid : Cu^{2+} = 1 : 3). Furthermore the Cu^{2+}-drug complexes associate with DNA to form the Cu^{2+}-anthraquinone-DNA ternary complexes. The formation of the complexes was further supported by the H_2O_2-dependent DNA degradation, which can be inhibited by ethidium bromide, caused by the Cu^{2+}-drug complexes. It is likely that the Cu^{2+}-mediated cytotoxicity of the anthraquinone drugs is related with the Cu^{2+}-mediated binding of the anthraquinone drugs to DNA and DNA degradation.

Introduction

Although the anthracyline antibiotics are believed to exert their antitumor action[1] by inhibiting DNA transcription and replication *via* intercalation of the anthracycline chromophore between DNA base pairs[2], their mechanism of action remains uncertain. The planar anthracycline chromophore, which can intercalate together with the positively charged amino-sugar moiety can be anticipated to provide a high DNA affinity. As is often the case with other intercalating agents[3,4], the DNA-topoisomerase II complex is presently believed to be the most probable target of the antitumor activity of the anthracyclines, resulting in DNA strand breakage. If the potent genotoxicity and antitumor activity of adriamycin (doxorubicin) could be attributable to its possession of planar aromatic chromophore which can intercalate between DNA base pairs, such anthraquinones as anthraquinone-1,5-disulfonic acid and carminic acid should also be expected to be able to be induced to attain DNA-intercalative form and consequently the anthracycline-like activity through the formation of appropriate positively charged metal chelate complex of the drugs, although their free drug forms are negatively charged and can not bind to DNA directly due to highly unfavorable electrostatic repulsive forces between the drug and the DNA molecules of the similar charge.

The idea described above prompted us to carry out a series of spectroscopic studies on the formation of the Cu^{2+}-drug complex, and interaction of the Cu^{2+}-drug complexes with DNA to form the ternary complexes. Cu^{2+}-drug-DNA; and consequent cytotoxicity of the Cu^{2+}-drug complexes against L1210 leukemia cells in culture and antitumor activity against Sarcoma 180 *in vivo*. Here we present some of the results.