Synthesis and Structure-Activity Relationship of Nonyl 3-Acyldithiocarbazates and Related Compounds for Uncoupling Activities

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Various nonyl 3-substituted-dithiocarbazates, methyl and dimethyl derivatives of nonyl 3-benzoyldithiocarbazate, nonyl 2-substituted-dithiocarbamates, and benzaldehyde nonyldithiocarbohydrazone were synthesized and their uncoupling activities of oxidative phosphorylation in mitochondria were examined. The results indicate that the presence of the thiocarbamoyl structure with the potential SH group is a requisite for uncoupling activity. The presence of a C=O group and a hydrophobic aromatic ring significantly increases the uncoupling activity.

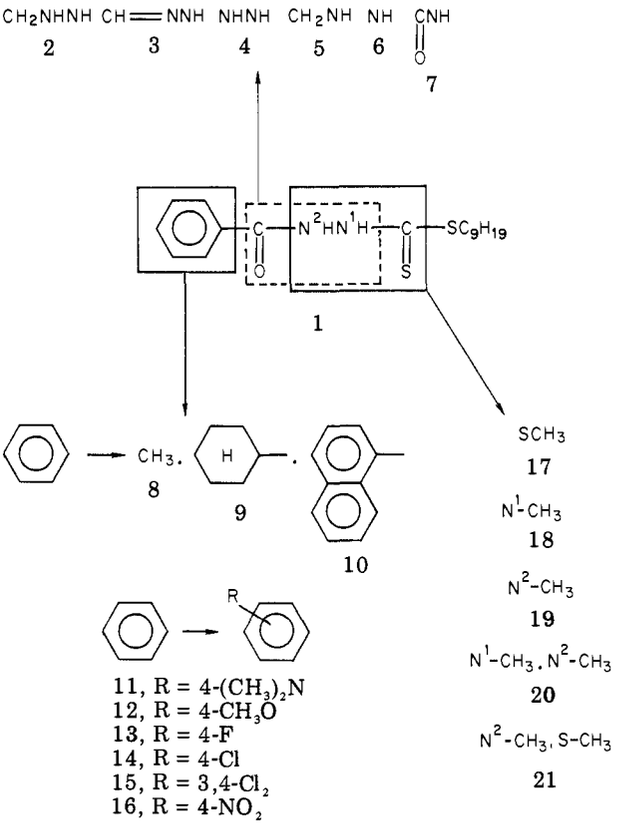
Various hydrophobic weak acids, such as phenols, salicylanilides, benzimidazoles, and phenylhydrazones, are known to be uncouplers of oxidative phosphorylation. Thus, the presence of an acid-dissociable group is regarded as indispensable for exhibiting uncoupling activity.

Recently, lipophilic isocyanates, such as 4-bromophenyl isothiocyanate, have been reported as a new class of uncouplers, because such compounds have no acidic proton.[1] However, these compounds were found to readily change into thioureas in dimethyl sulfoxide, which was used as a solvent for the stock solution of isothiocyanates, and the resulting thioureas were actually active.[2] *N*-Alkylthioureas and 6-alkyl-2-thiouracil have been reported as another class of inhibitors of oxidative phosphorylation.[3]

We have previously reported the uncoupling activities on oxidative phosphorylation of *S*-alkyl pyridinecarbonyldithiocarbazates in mitochondria.[4-6] These compounds possess the potentially tautomeric thiocarbamoyl moiety, NHCS, as in thioureas and thiouracils. Therefore, dithiocarbazates, thioureas, and thiouracils can be classified as weakly acidic uncouplers with the potential SH group.

In the present study, to establish the structure–activity relationship of nonyl 3-acyldithiocarbazates for their uncoupling activities, we used nonyl 3-benzoyldithiocarbazate (**1**) as a parent compound for structural modifications, since its uncoupling activity was similar to those of nonyl pyridinecarbonyldithiocarbazates.[7] This paper describes the syntheses of modified compounds of **1** and their structure–activity relationships on uncoupling activities (Scheme I).

Scheme I



Chemistry. Various compounds used in the present study were synthesized by the methods shown in Scheme II. The nonyl 3-acyldithiocarbazates (**1** and **8–16**) were synthesized by the reaction of the appropriate acid hydrazide with carbon disulfide, followed by S-alkylation with nonyl iodide by a method similar to that described previously.[5] Compounds **4–6** were also prepared by the same method as that for **1** using phenylhydrazine, benzylamine, and aniline, respectively, instead of acid hydrazide. The same reaction using benzylhydrazine as a starting material gave two products, the desired product (**2**) and its isomer (**22**), which were separated by silica gel column chromatography. Compound **7** was synthesized by reactions of nonanethiol with benzoyl isothiocyanate.[8] Compound **3** was prepared by condensation of nonyl dithiocarbazate[5] with benzaldehyde.

The *S*-methyl derivative (**17**) of **1** was prepared by methylation of **1** with methyl iodide in alkaline solution. The *N*-methyl derivatives (**18–20**) were synthesized from 1-benzoyl-2-methylhydrazine,[9] 1-benzoyl-1-methylhydrazine,[9] and 1-benzoyl-1,2-dimethylhydrazine, respectively, by the same method as that for the synthesis of **1**. 1-Benzoyl-1,2-dimethylhydrazine was prepared by the reaction of 1,2-dimethylhydrazine with benzoic anhydride. Methylation of **19** with methyl iodide in alkaline solution gave the *N*,*S*-dimethyl derivative (**21**).

Uncoupling Activity. Uncoupling activities of nonyl 3-acyldithiocarbazates (**1**, **8–16**, and **18–20**) and their related compounds (**2–7**, **17**, and **21**) were determined by measuring changes in state 4 respiration of rat liver mitochondria using succinate (plus rotenone) as substrate and were shown as the concentration required for maximal release of the respiration. Relative activities (RA) of compounds **2–21** are based on the activity of **1** being 100%

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Table I. Physical Data and Uncoupling Activity of Dithiocarbazates and Their Related Compounds

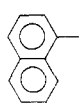
X—CS(=S)—C_9H_{19}

no.	X	yield, %	mp, °C	formula[a]	C_{100},[b] μM	RA[c]
1	$C_6H_5CONHNH$	27	83.5-84.0	$C_{17}H_{26}N_2OS_2$	1.59	100
2	$C_6H_5CH_2NHNH$	24	48.0-50.0	$C_{17}H_{28}N_2S_2$	8351	0.02
3	$C_6H_5CH{=}NNH$	82	92.0-93.0	$C_{17}H_{26}N_2S_2$	604	0.26
4	C_6H_5NHNH	80	96.0-97.0	$C_{16}H_{26}N_2S_2$	1530	0.10
5	$C_6H_5CH_2NH$	37	37.0-38.0	$C_{17}H_{27}NS_2$	360	0.44
6	C_6H_5NH	23	54.0-55.0	$C_{16}H_{25}NS_2$	inact	0.00
7	C_6H_5CONH	63	38.0-39.0	$C_{17}H_{25}NOS_2$	27.9	5.70
	$2\text{-}C_6H_4NCONHNH$[d]				1.42	112

[a] All compounds were analyzed for C, H, and N within 0.3% of the theoretical values. [b] The concentration required for the maximal release of state 4 respiration of rat liver mitochondria using succinate (+ 1 μg/mg of the protein rotenone) as substrate (see Experimental Section). [c] Relative activity: the activity of 1 is taken as a standard. [d] References 4-6.

Table II. Physical Data and Uncoupling Activity of Dithiocarbazates and Their Related Compounds

Y—CONHNHCS(=S)—C_9H_{19}

no.	Y	yield, %	mp, °C	formula[a]	C_{100},[b] μM	RA[c]
8	CH_3	31	76.0-77.0	$C_{12}H_{24}N_2OS_2$	457	0.61
9		22	80.0-81.0	$C_{17}H_{32}N_2OS_2$	4.52	35.00
10		24	83.0-85.0	$C_{21}H_{28}N_2OS_2$	3.36	47.00

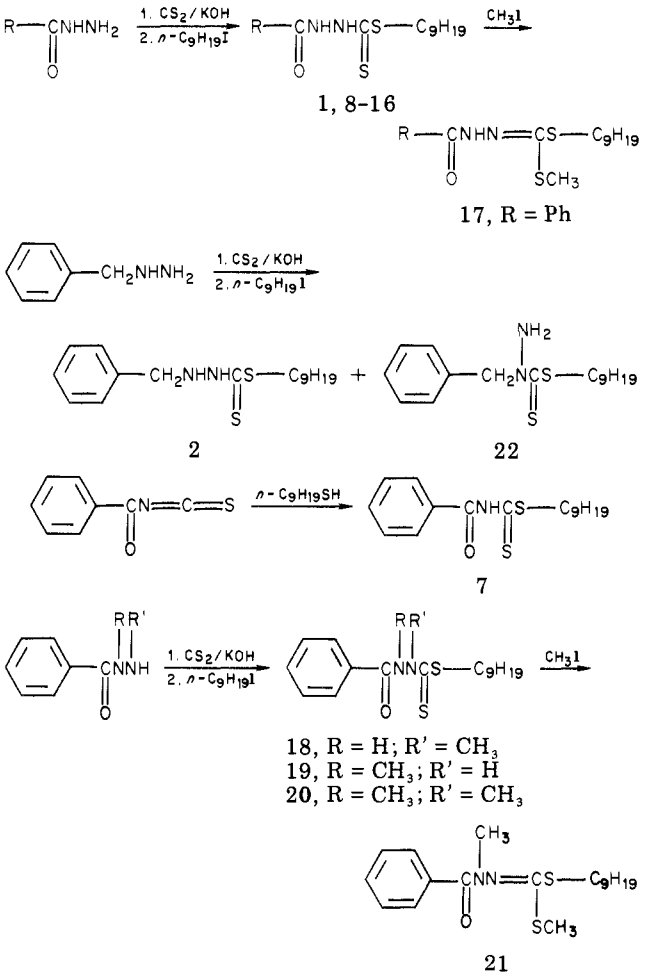
[a] All compounds were analyzed for C, H, and N within 0.3% of the theoretical values. [b,c] See corresponding footnotes in Table I.

active, as listed in Tables I–IV.

By comparing the activity of 1 with those of 2–4, we found that any modification of the C=O group of 1 such as replacement by CH_2, conversion into CH=, and removal, caused a remarkable decrease in the activities of the resulting compounds, in spite of no significant differences in the size of the molecules and their hydrophobicity (Table I). These results suggest that the C=O group in the molecule plays a role in retaining moderate acidity, which is very important for exhibiting the biological activity. Removal of one of the adjacent NH groups of 1, as in 5–7, decreases the activity, even though 7 has a C=O group.

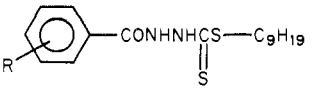
In order to study which acyl group is the most effective, three types of acyl derivatives of nonyl dithiocarbazates, the simple aliphatic acyl derivative (8), the cyclo-aliphatic acyl derivative (9), and the aromatic acyl derivative (10), were tested for uncoupling activities. As shown in Table II, the aromatic acyl derivative (10) was found to be the most active, but none of them was more active than 1.

Scheme II



Therefore, the structure of compound 1 was taken as the basic structure for the activity (Table II).

Table III. Physical Data and Uncoupling Activity of Dithiocarbazates and Their Related Compounds



no.	R	yield, %	mp, °C	formula[a]	C_{100},[b] μM	RA[c]
11	$4\text{-}(CH_3)_2N$	51	164.0-165.0	$C_{19}H_{31}N_3OS_2$	6.90	23
12	$4\text{-}CH_3O$	24	122.0-123.0	$C_{18}H_{28}N_2O_2S_2$	2.46	65
13	4-F	31	105.0-106.0	$C_{17}H_{25}N_2OS_2F$	1.57	101
14	4-Cl	23	109.0-110.0	$C_{17}H_{25}N_2OS_2Cl$	1.46	109
15	$3,4\text{-}Cl_2$	27	115.0-116.5	$C_{17}H_{24}N_2OS_2Cl_2$	1.93	82
16	$4\text{-}NO_2$	21	123.0-124.0	$C_{17}H_{25}N_3O_3S_2$	1.27	125

[a] All compounds were analyzed for C, H, and N within 0.3% of the theoretical values. [b,c] See corresponding footnotes in Table I.

Table IV. Physical Data and Uncoupling Activity of Dithiocarbazates and Their Related Compounds

	Z—S—C_9H_{19}					
no.	Z	yield, %	mp, °C	formula[a]	C_{100},[b] μM	RA[c]
17	$C_6H_5CONHN{=}C(SCH_3)$-	34	oil	$C_{18}H_{28}N_2OS_2$	30.1	9.30
18	$C_6H_2CONHN(CH_3)C(=S)$-	25	60.0-61.0	$C_{18}H_{28}N_2OS_2$	40.3	6.90
19	$C_6H_5CON(CH_3)NHC(=S)$-	43	48.5-50.0	$C_{18}H_{28}N_2OS_2$	112	1.30
20	$C_6H_5CON(CH_3)N(CH_3)C(=S)$-	16	oil	$C_{19}H_{30}N_2OS_2$	inactive	0.00
21	$C_6H_5CON(CH_3)N{=}C(SCH_3)$-	52	oil	$C_{19}H_{30}N_2OS_2$	inactive	0.00

[a] All compounds were analyzed for C, H, and N within 0.3% of the theoretical values. [b,c] See corresponding footnotes in Table I.

Further, these results prompted us to examine the effect of substituents at the 4 position in the benzoyl group of **1** for uncoupling activity on mitochondria. The data in Table III indicate that the introduction of electron-donating groups, such as dimethylamino (**11**) and methoxy (**12**), decreases the activity. On the other hand, contrary to expectation, the introduction of electron-withdrawing groups, such as fluoro (**13**), chloro (**14** and **15**), and nitro (**16**), does not increase the activity significantly.

Furthermore, in order to study the role of acidic protons in activity, we have replaced the NH or potential SH proton with a methyl group and examined the uncoupling activity. The monomethylated derivatives (**17–19**) having the NH or SH proton were found to be weakly active, while the dimethylated derivatives (**20–21**) having no acidic proton were completely inactive. These results are in agreement with our previous prediction[6] that the presence of a dissociable proton is essential for the activity of dithiocarbazates (Table IV).

On the basis of all these data, it was concluded that the presence of the thiocarbamoyl structure with the potential SH group is essential for the uncoupling activity of acyl dithiocarbazates, and the presence of the C=O group and the hydrophobic aromatic ring is also a requisite for high activity.

Experimental Section

Melting points were determined by the capillary method and are uncorrected. NMR spectra were recorded with a JEOL PS-100 spectrometer using tetramethylsilane as an internal standard. Mass spectra were obtained on a JEOL-D300 spectrometer. Column chromatography was performed with a mixture of 50% of Merck silica gel 60 (70–230 mesh) and 50% of Mallinckrodt silicic acid (100 mesh). The yields and melting points are listed in Tables I–IV.

Nonyl 3-Benzoyldithiocarbazate (1). Carbon disulfide (4.56 g, 60 mmol) was added to a stirred mixture of benzhydrazide (4.08 g, 30 mmol) in EtOH (18 mL) and KOH (1.7 g) in H_2O (1.5 mL), and the reaction mixture was stirred at room temperature for 1 h. Nonyl iodide (7.62 g, 30 mmol) was added dropwise under cooling, and the mixture was stirred overnight at room temperature and then extracted with $CHCl_3$. The $CHCl_3$ layer was dried over Na_2SO_4 and evaporated in vacuo. Column chromatography of the residual viscous oil on silica gel with C_6H_{14}–C_6H_6 (3:4) gave a solid, which was recrystallized from isopropyl ether as a colorless needles: yield 2.74 g (27%).

Nonyl 3-Benzyldithiocarbazates (2). Carbon disulfide (1.99 g, 26 mmol) was added to a stirred mixture of benzylhydrazine (1.6 g, 13 mmol) in EtOH (5 mL) and KOH (0.93 g) in H_2O (1 mL). Nonyl iodide (3.3 g, 13 mmol) was added dropwise under cooling, and the mixture was stirred overnight at room temperature and then extracted with $CHCl_3$. The $CHCl_3$ layer was dried over Na_2SO_4 and evaporated. Column chromatography of the residual oil on silica gel using C_6H_6–$CHCl_3$ (1:1) gave two fractions. Evaporation of the solvent from the first fraction gave an oily residue, which was crystallized from isopropyl ether to give colorless needles of **2**: yield 1.02 g (24%); IR (KBr) 3150 (NH) cm^{-1}. Evaporation of the solvent from the second fraction gave an oily residue, which was crystallized from isopropyl ether to give colorless needles of **22**: yield 0.11 g; mp 66–67 °C; IR (KBr) 3300, 1600 (NH) cm^{-1}. Anal. ($C_{17}H_{28}N_2S_2$) C, H, N.

Benzaldehyde Nonyldithiocarbohydrazone (3). Benzaldehyde (0.53 g, 5 mmol) was added to a solution of nonyl dithiocarbazate[5] (1.17 g, 5 mmol) in EtOH (25 mL), and the mixture was refluxed for 2 h. After the mixture was cooled, the resulting precipitate was collected by filtration and crystallized from EtOH to give colorless needles: yield 1.32 g (82%).

Nonyl 3-Phenyldithiocarbazate (4). Carbon disulfide (1.71 g, 23 mmol) was added to a stirred mixture of phenylhydrazine (1.62 g, 15 mmol) in EtOH (18 mL) and KOH (0.84 g) in H_2O (1.5 mL), and the reaction mixture was stirred for 1 h at room temperature. After that, nonyl iodide (3.81 g, 15 mmol) was added dropwise, and the mixture was stirred overnight at room temperature. The resulting precipitate was collected by filtration and crystallized from isopropyl ether as colorless needles: yield 3.72 g (80%).

Nonyl 2-Benzyldithiocarbamate (5). Compound **5** was prepared from benzylamine (3.0 g, 28 mmol) by the same procedure as that for **1**. The product was crystallized from isopropyl ether as colorless needles: yield 3.2 g (37%).

Nonyl 2-Phenyldithiocarbamate (6). Compound **6** was prepared from aniline (3.0 g, 32 mmol) by the same procedure as that for **1**. The product was crystallized from isopropyl ether as colorless needles: yield 2.2 g (23%).

Nonyl 2-Benzoyldithiocarbamate (7). Benzoyl chloride (2.81 g, 20 mmol) was added to a solution of potassium thiocyanate (1.94 g, 20 mmol) in acetonitrile (15 mL), and the mixture was refluxed for 15 min. After the mixture was cooled nonanethiol (3.21 g, 20 mmol) was added to the mixture under stirring. The reaction mixture was stirred overnight at room temperature and then extracted with $CHCl_3$ (50 mL × 2). The $CHCl_3$ layer was dried over Na_2SO_4 and evaporated in vacuo. Column chromatography of the residual oil on silica gel with C_6H_{14}–C_6H_6 (1:1) gave a solid, which was crystallized from isopropyl ether as colorless crystals: yield 3.3 g (63%).

Nonyl 3-Acyldithiocarbazates (8–16). Compounds **8–16** were prepared by a method similar to that for **1**. The following solvents were used for crystallization of the compounds: **8**, ether; **9**, **10**, **13**, **15**, and **16**, isopropyl ether; **11**, EtOH–$CHCl_3$; **12**, isopropyl ether–$CHCl_3$; **14**, EtOH.

***S*-Methyl-*S'*-nonyl *N*-Benzoylcarbonohydrazonodithioate (17).** A mixture of methyl iodide (1.14 g, 1 mmol) and EtOH (1 mL) was added to a solution of **1** (0.34 g, 1 mmol) in 1 N NaOH (1 mL) and then stirred overnight at room temperature. The mixture was poured into H_2O (15 mL) and extracted with $CHCl_3$ (15 mL × 2). The $CHCl_3$ extract was dried over $NaSO_4$ and evaporated. Column chromatography of residual oil on silica gel with $CHCl_3$–C_6H_6 (1:1) gave the product (**17**) as a colorless oil: yield 0.12 g (34%); NMR ($CDCl_3$) δ 2.50 (s, 3 H, SCH_3); mass spectrum, *m/e* 352.1643 (calcd for $C_{18}H_{28}N_2OS_2$, 352.1643).

Nonyl 3-Benzoyl-2-methyldithiocarbazate (18). Compound **18** was prepared from 1-benzoyl-2-methylhydrazine[9] (1.5 g, 10 mmol) by the same procedure as that for **1**. The product was crystallized from isopropyl ether as colorless crystals: yield 0.9 g (25%); NMR ($CDCl_3$) δ 3.70 (s, 3 H, NCH_3).

Nonyl 3-Benzoyl-3-methyldithiocarbazate (19). Compound **19** was prepared from 1-benzoyl-1-methylhydrazine[9] (3.0 g, 20 mmol) by the same procedure as that for **1**. The product was crystallized from isopropyl ether as colorless crystals: yield 3.0 g (43%); NMR ($CDCl_3$) δ 3.30 (s, 3 H, N-CH_3).

1-Benzoyl-1,2-dimethylhydrazine. Benzoic anhydride (2.33 g, 10.3 mmol) was added portionwise to a stirred solution of 1,2-dimethylhydrazine (0.617 g, 10.3 mmol) in water (3 mL) during 1 h under cooling. After 30 min, the mixture was extracted with $CHCl_3$ (50 mL × 2). The organic layer was washed with water,

dried over Na_2SO_4, and evaporated to dryness in vacuo to give a crystalline product as a salt of benzoic acid. Column chromatography of the salt on silica gel with $CHCl_3$–MeOH (10:1) gave a free base as an oil: yield 1.2 g (71%); bp 132 °C (1 mmHg); mass spectrum, *m/e* 164.0994 (calcd for $C_9H_{12}N_2O$, 164.0949).

Nonyl 3-Benzoyl-2,3-dimethyldithiocarbazate (20). Compound **20** was prepared from 1-benzoyl-1,2-dimethylhydrazine (1.32 g, 8 mmol) by the same procedure as that for 1. The product was obtained as a colorless viscous oil: yield 0.47 g (16%): NMR($CDCl_3$) δ 3.26 (s, 3 H, N^2-CH_3), 3.39 (s, 3 H, N^3-CH_3); mass spectrum *m/e* 366.1768 (calcd for $C_{19}H_{30}N_2OS_2$, 366.1799).

***S*-Methyl-*S'*-nonyl *N*-Benzoyl-*N*-methylcarbonohydrazonodithioate (21).** Compound **21** was prepared by methylation of **19** with methyl iodide by the same procedure as that for 17. The product was obtained as a colorless viscous oil: NMR ($CDCl_3$) δ 2.44 (s, 3 H, S-CH_3), 3.20 (s, 3 H, N-CH_3); mass spectrum, *m/e* 367.1871 (MH^+) (calcd for $C_{19}H_{31}N_2OS_2$, 367.1877).

Uncoupling Activity. Rat liver mitochondria were isolated as described previously.[10] The change in the respiratory rate of state 4 mitochondria on addition of test compound was monitored with a Clark oxygen electrode (Yellow Spring Instruments) with 10 mM succinate (plus 1 μg/mg of the protein rotenone) as substrate in an incubation medium consisting of 200 mM sucrose, 2 mM $MgCl_2$, 1 mM EDTA, and 10 mM potassium phosphate buffer, pH 7.2, at 25 °C. The amount of mitochondria was, in most cases, 0.7 mg/mL, and the volume of the reaction mixture was 4.35 mL. The uncoupling activity of the test compound was determined as the concentration required for maximal release of the respiration of mitochondria.

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Structure-Activity Relationships of Nogalamycin Analogues[1]

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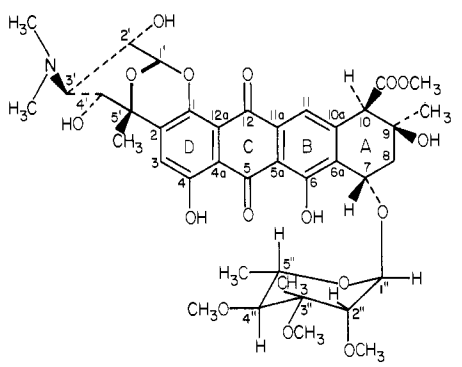
Nogalamycin (1) has been modified by changes at C-10 and C-7 and in the dimethylamino group to prepare an extensive series of analogues. The chemistry involved in the modifications and structure–activity relationships among these nogalamycin analogues are discussed, as well as comparisons with previously reported compounds 1, 7-con-*O*-methylnogarol (**2**), and disnogamycin (11).

Nogalamycin (**1**) is an antibiotic of the anthracycline



1

family, and it, as is typical of members of this family, has long been known as an antitumor agent.[2] Because of the outstanding antitumor activity of Adriamycin and daunomycin, two members of the anthracycline family, it seemed worthwhile to prepare by chemical modification an extensive series of analogues of 1. Very early in this work it was found that replacement of the neutral sugar of 1 by various alkoxy groups gave compounds with considerable antitumor activity.[3] One of the members of this group, 7-con-*O*-methylnogarol (**2**), has been found to be sufficiently active that phase I clinical trials will be initiated in the near future. Introduction of groups other than alkoxy at C-7 in 1 and in disnogamycin (11) appeared warranted and are reported in this article, as are modifications involving the carbomethoxy group at C-10, the dimethylamino group, and acylation and alkylation of hydroxyl groups. The structure–activity relationships of these compounds based on in vitro cytotoxicity and in vivo activity against a murine leukemia are discussed.

Chemistry. The preparation of a series of analogues in which the carbomethoxy group at C-10 has been retained (the nogalarol series) and in which it has been removed (the nogarol series) and in which nogalose has been replaced by alkoxy groups has been reported.[1,4] Four more compounds of this type are reported here. Three of these (**3–5**) were prepared by the trifluoroacetic acid procedure previously reported[4] in which only the con[5] isomer is formed. In this reaction, disnogamycin (11) is treated with trifluoroacetic acid, followed by treatment with nucleophiles, which for these compounds were alkoxide anions. As has been the case previously, molecular ions in the mass

(1) A portion of this work has been published previously. See Wiley, P. F. *J. Nat. Prod.* **1979**, *42*, 569.
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(5) Structure 1 is assigned to nogalamycin based on X-ray crystallography of **2** and on an extensive series of circular dichroism studies.[4] The X-ray studies have provided only relative stereochemistry, and it is felt that aside from the nogalose moiety, absolute stereochemistry is not sufficiently established to use *R* and *S* designations for compounds isomeric at C-7. Consequently, nomenclature is not based on absolute stereochemistry at C-7 and C-9 but on relative stereochemistry. Those compounds in which hydroxyls at C-9 and C-7 are cis are called con. If these groups are trans, the prefix dis is used. The cis–trans nomenclature was not used because a third group, the amino sugar, can also be cis or trans to a substituent at C-7. **Note Added in Proof:** Dr. S. K. Arora of the University of Arizona has recently established the complete stereochemistry of 1 by X-ray crystallography studies. C-7, C-9, and C-10 are *S*, *S*, and *R*, respectively, with the amino sugar having the α-L configuration. Because of these findings, the nomenclature has been changed so that con compounds are 7*R* and dis compounds are 7*S*.

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