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Antiulcer Activity of Dehydroabietic Acid Derivatives

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Derivatives of dehydroabietic acid (**1**) having a hydrophilic moiety (such as amino, carbamoyl, carbamoyloxy, ureido, sulfamoyl, or sulfo) at positions 12 and/or 18 of the dehydroabietane nucleus were prepared and tested for antiulcer activity by means of antisecretory and antipepsin assays in rats. Among these compounds, the salts of 12-sulfodehydroabietic acid (**62**, **63**, and **64**) were found to exhibit remarkably high antipepsin activity without aldosterone-like activity.

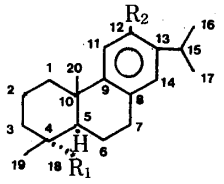
Keywords——dehydroabietic acid; diterpene; antisecretory action; antipepsin activity; antiulcer; structure–activity relationship

Antiulcer agents such as gefarnate and carbenoxolone sodium (**23**) derived from terpenoid sources are clinically useful in view of their mucosal protective property. However, carbenoxolone sodium (**23**) has pronounced mineralocorticoid-like activity and shows the side effects of fluid retention, hypokalaemia, and raised blood pressure, which limit its clinical usefulness.[1,2] Baran *et al.*[3] reported some modifications of glycyrrhetinic acid (the nucleus of carbenoxolone) in an attempt to separate these side effects from the antiulcer activity.

As part of a program aimed at discovering new antiulcer agents with enhanced cytoprotective effect, we were interested in determining whether or not the dehydroabietane nucleus could act as a substitute for the oleanane skeleton of carbenoxolone sodium (**23**) with fewer side effects. Many attempts have been made to prepare biologically active compounds[4,5] from dehydroabietic acid (**1**). For example, Fujita *et al.*[6] reported the hypocholesterolemic activity of abietamide derivatives. However, no reports have appeared on the antiulcer activity of dehydroabietic acid derivatives. We describe here the syntheses of a number of derivatives of dehydroabietic acid (**1**), which is readily available from disproportionated rosin, and the results of preliminary evaluation of their antiulcer activities as determined by means of antisecretory and antipepsin assays in rats.[7] In this study, a hydrophilic moiety (such as amino, carbamoyl, carbamoyloxy, ureido, sulfo, or sulfamoyl) was introduced into the lipophilic dehydroabietane skeleton.

Chemistry

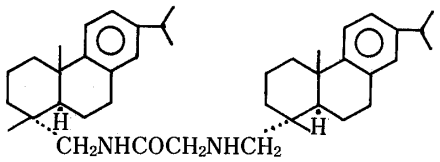
All the compounds listed in Tables I—IV were derived from either dehydroabietic acid (**1**)[8] or 12-sulfodehydroabietic acid (**15**) by standard methods or known procedures. These starting materials were prepared from commercially available disproportionated pine rosin by the method described by Fieser and Campbell.[9] The three key intermediates for the syntheses of the compounds listed in Table I, dehydroabietyl alcohol (**2**), the acid chloride (**3**), and the isocyanate (**4**),[10] were prepared from **1**. The modified Curtius reaction using diphenyl



1: $R_1=COOH$, $R_2=H$
2: $R_1=CH_2OH$, $R_2=H$
3: $R_1=COCl$, $R_2=H$
4: $R_1=NCO$, $R_2=H$
5: $R_1=CH_2OCOCl$, $R_2=H$
6: $R_1=CH_2NH_2$, $R_2=H$
7: $R_1=CH_2NHMe$, $R_2=H$
8: $R_1=CH_2NH(CH_2)_2NMe_2$, $R_2=H$
9: $R_1=CH_2NHCOCH_2Cl$, $R_2=H$
10: $R_1=CONMe_2$, $R_2=H$
11: $R_1=CONHCH(COOH)(CH_2)_2SMe$, $R_2=H$
13: $R_1=CONH(CH_2)_2CN$, $R_2=H$
14: $R_1=CONH(CH_2)_2CSNH_2$, $R_2=H$
15: $R_1=COOH$, $R_2=SO_3H$
16: $R_1=COOH$, $R_2=SO_2Cl$
18: $R_1=COOH$, $R_2=SO_3Me$
19: $R_1=CONHMe$, $R_2=SO_3Me$
20: $R_1=CSNHMe$, $R_2=SO_3Me$
21: $R_1=CH_2OH$, $R_2=SO_3H$

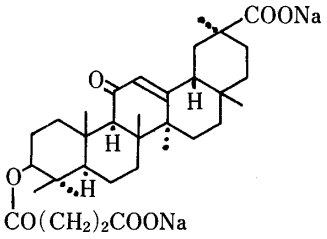
12: $R_1=CONH(CH_2)_2CONHCH(COOMe)CH_2$ (imidazole-NH), $R_2=H$

17: $R_1=CONH(CH_2)_2CONHCH(COOMe)CH_2$ (imidazole-NH), $R_2=SO_3H$

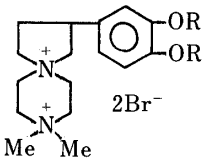


22

Chart 1



23



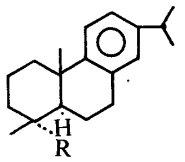
24: R=H
25: R=Me

Chart 2

phosphorazidate (DPPA)[11] was conveniently used for the preparation of **4**.

Compound **2** was alkylated with 3-(chloropropyl)dimethylamine to give the ether (**26**). Reaction of **2** with phosgene afforded the chloroformate (**5**), which was condensed with various amines to give the corresponding urethanes (**27**—**29**). The *N*-methyl amine (**30**) was obtained by the reduction of **4** with lithium aluminum hydride (LAH) according to the method of Zeiss.[10] Treatment of **4** with morpholine, aniline, and 3-(dimethylamino)-propylamine gave the corresponding ureas (**31**—**33**). *N*-[2-(Dimethylamino)ethyl]dehydroabietamide (**34**), prepared from **3** by means of the Schotten–Baumann reaction, was reduced with LAH to the diamine (**8**). Acylation of **8** with *N*,*N*-dimethylcarbamoyl chloride gave

TABLE I.



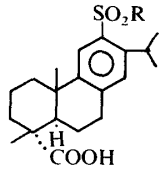
1, **26**—**39**

No.	R	Yield (%)	mp (°C)	Analysis (%) Calcd (Found)			Antisecretory activity % inhibition *i.p.* at 30 mg/kg	Antipepsin activity % inhibition *i.g.* at 100 mg/kg
				C	H	N		
26	$CH_2O(CH_2)_3NMe_2$	42	95—96	$C_{25}H_{41}NO \cdot C_6H_8O_7 \cdot 1/2H_2O$			86	17
				65.01	8.97	2.45		
				(65.02	8.57	2.63)		
27	$CH_2OOCNH(CH_2)_2NMe_2$	49	147—149	$C_{25}H_{40}N_2O_2 \cdot C_2H_2O_4$			83	24
				66.09	8.62	5.71		
				(66.38	8.82	5.76)		
28	CH_2OOCN O	95	105—106	$C_{25}H_{37}NO_3$			43	−33
				75.14	9.33	3.51		
				(75.18	9.51	3.52)		
29	CH_2OOCN NMe	70	217—220	$C_{26}H_{40}N_2O_2 \cdot HCl$			55	28
				69.53	9.20	6.23		
				(69.84	9.53	5.88)		
30	NHMe	95	196—199	$C_{20}H_{31}N \cdot HCl$[a]			81	69
31	NHCON O	71	155—156	$C_{24}H_{36}N_2O_2$			51	9
				74.95	9.43	7.28		
				(74.74	9.64	6.89)		

32	$NHCONHC_6H_5$	51	197—199	$C_{26}H_{34}N_2O$ 79.95 8.78 7.17 (79.72 8.80 7.13)	72	10
33	$NHCONH(CH_2)_3NMe_2$	58	Amorph.	$C_{25}H_{41}N_3O$[a]	49	10
34	$CONH(CH_2)_2NMe_2$	63	95—98	$C_{24}H_{38}N_2O \cdot HCl$ 70.91 9.67 6.94 (70.67 9.33 6.80)	72	32
35	$CH_2N(CH_2)_2NMe_2$ $CONMe_2$	74	157	$C_{27}H_{45}N_3O \cdot HCl \cdot 1/2MeOH$ 68.82 10.01 8.76 (68.64 9.63 8.83)	83	37
36	$CH_2NCSNH(CH_2)_2NMe_2$ Me	92	157—159	$C_{26}H_{43}N_3S \cdot HCl$ 66.98 9.51 9.01 (66.80 9.15 9.00)	87	−35
37	$CH_2NHCOCH_2N(n\text{-}Pr)_2$	81	89—91	$C_{28}H_{46}N_2O \cdot C_4H_4O_4$ 70.81 9.29 5.16 (70.85 9.32 4.78)	83	34
38	$CH_2NHCOCH_2N$ 	96	175—177 (dec.)	$C_{27}H_{42}N_2O \cdot C_2H_2O_4 \cdot 1/2MeOH$ 68.55 8.97 5.42 (68.20 8.99 5.43)	80	13
39	$CH_2NHCOCH_2N$	95	197—200 (dec.)	$C_{26}H_{40}N_2O_2 \cdot C_2H_2O_4 \cdot 1/2MeOH$ 66.38 8.94 5.40 (66.12 8.53 5.51)	66	22
1	COOH	72	168—171	$C_{20}H_{28}O_2$ 80.07 9.41 (80.26 9.44)	22	−4
23	Carbenoxolone sodium				77	71

a) The structure of this compound was assigned on the basis of spectrometric methods.

TABLE II.



40—49

No.	R	Yield (%)	mp (°C)	Analysis (%) Calcd (Found)			Antisecretory activity % inhibition *i.p.* at 30 mg/kg	Antipepsin activity % inhibition *i.g.* at 100 mg/kg
				C	H	N		
40	NH_2	72	296—299	$C_{20}H_{29}NO_4S$			−8	−10
				63.38	7.71	3.70		
				(63.40	7.45	3.62)		
41	$NH(CH_2)_2NMe_2$	37	278—280 (dec.)	$C_{24}H_{38}N_2O_4S \cdot HCl \cdot 1/2H_2O$			63	−20
				58.17	7.93	5.65		
				(58.54	7.88	5.42)		
42	$NH(CH_2)_2NH_2$	52	241—244	$C_{22}H_{34}N_2O_4S \cdot 1/2H_2O$			37	−11
				61.30	8.19	6.50		
				(60.95	8.39	6.22)		
43	$NH\text{–}C_6H_{11}O_5$[a]	28	177—180 (dec.)	$C_{26}H_{41}NO_9S \cdot 1/2H_2O$			−16	55
				56.57	7.85	2.54		
				(56.71	7.41	2.47)		
44	$NH(CH_2)_2NHCSNHMe$	64	227—228	$C_{24}H_{37}N_3O_4S_2$			−31	−2
				58.23	7.53	8.49		
				(58.27	7.57	7.95)		
45	$NHCSNH(CH_2)_2NMe_2$	38	173—175 (dec.)	$C_{25}H_{39}N_3O_4S_2 \cdot H_2O$			−16	31
				56.97	7.84	7.79		
				(57.46	7.69	7.73)		
46	$NH(CH_2)_2CO_2H$	44	234—235 (dec.)	$C_{23}H_{33}NO_6S$			10	2
				61.17	7.37	3.10		
				(60.99	7.30	3.04)		
47	$NHCH(CH_2)_2CONH_2$ COOH	28	255 (dec.)	$C_{25}H_{36}N_2O_7S$			−7	−9
				59.03	7.13	5.51		
				(58.71	7.29	5.36)		
48	$NHCH(COOH)CH_2Ph$	68	260—262 (dec.)	$C_{29}H_{37}NO_6S$			3	−8
				66.01	7.07	2.66		
				(66.01	7.12	2.67)		
49	NHPh(4-COOH)	60	>300	$C_{27}H_{33}NO_6S$			25	−13
				64.91	6.66	2.80		
				(64.66	6.81	2.79)		

a) The formula denotes a 2-amino, 2-deoxy glucosyl residue.

the urea (**35**). The thiourea (**36**) was easily prepared from *N*-methyldehydroabietylamine[12] (**7**) by treatment with 2-(dimethylamino)ethyl isothiocyanate[13] in good yield. The chloroacetamide (**9**), derived from dehydroabietylamine[12] (**6**) with chloroacetyl chloride,[14] was aminated with various amines to give the corresponding 2-aminoacetamide derivatives (**37**—**39**).

We next prepared compounds bearing two functional groups, one at each end of the dehydroabietane skeleton, as in the case of carbenoxolone sodium (**23**). Except for **44** and **45**, the 12-sulfonamide derivatives listed in Table II were prepared by condensation of 12-(chlorosulfonyl)dehydroabietic acid (**16**) with appropriate amines, amino acids, or amino-sugar. The thiourea derivative (**44**) was obtained by condensation of the *N*-(2-aminoethyl)sulfonamide (**42**) with methyl isothiocyanate. Similarly, the sulfonylthiourea (**45**) was prepared by the reaction of the sulfonamide (**40**) with 2-(dimethylamino)ethyl isothiocyanate. Compound (**16**) was obtained from 12-sulfodehydroabietic acid 12-sodium salt (**62**) by chlorination with phosphorus pentachloride followed by partial hydrolysis.

The third group of derivatives (Table III) has a sulfonic acid group at the C-12 position and various additional functions, which would be expected to contribute to antiulcer activity, at the C-4 position. These compounds (**50**—**54**) were synthesized by the sulfonation of the corresponding dehydroabietane derivatives (**8**, **30**, and **35**—**37**) with cold concentrated sulfuric acid. *N*,*N*-Dimethyldehydroabietamide (**10**)[12] and *N*-(dehydroabietoyl)methionine (**11**) were prepared by the reaction of **3** with dimethylamine and methionine, respectively. Sulfonation of **10** or **11** gave **55** or **56**, respectively.

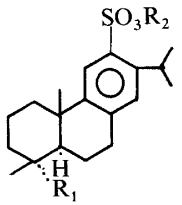
Methylation of **56** with methyl iodide[15] gave the *S*-methylmethioninesulfonium inner salt (**57**). Acylation of methyl carnocinate with **3** afforded the amide ester (**12**). Sulfonation of **12** gave the sulfonic acid (**17**), which was converted to the diacid (**58**) by alkaline hydrolysis. The thioamide (**59**) was prepared from the corresponding dehydroabietamide derivative (**14**) by the sulfonation procedure described above. Reaction of **3** with 2-cyanoethylamine followed by treatment with *O*,*O*′-diethyl dithiophosphate[16] gave **14**. An attempt to convert the intermediate (**13**) to **14** by the use of hydrogen sulfide in pyridine was unsuccessful. The methylsulfonate (**18**), prepared from **16**, was converted to the *N*-methyl amide (**19**) through the acid chloride. Treatment of **19** with phosphorus pentasulfide followed by alkaline hydrolysis gave the *N*-methyl thioamide (**60**). Reduction of 12-sulfodehydroabietic acid (**15**) with excess LAH gave 12-sulfodehydroabietyl alcohol (**21**), which was acylated with succinic anhydride to give 12-sulfodehydroabietyl hydrogen succinate (**61**) bearing a side chain analogous to that of carbenoxolone sodium (**23**).

Since the sodium salt of 12-sulfodehydroabietic acid (**15**) showed potent antipepsin activity (see below), a wide variety of the salts of **15** (listed in Table IV) was prepared in order to examine the effect of the cationic part. These compounds were generally prepared from **15** with one or two equivalents of base (Method A). Compounds **64**—**66** were obtained from the disodium salt (**63**) by treatment with the appropriate metal halides (Method B). The *S*-methylmethioninesulfonium (**72**) and spiro-ammonium (**73**) salts were obtained by exchange reaction of the silver salt of **15** with the corresponding sulfonium iodide[15] and the diazaspirodecanium dibromide (**24**),[17] respectively (Method C). The required cation (**24**) was prepared by demethylation of the dimethyl ether (**25**)[18a] with hydrobromic acid. The cationic component of the salt (**74**) was synthesized from 4-phenyl-2-pyrrolidinone according to the reported procedure.[18b]

Biological Methods

Male Sprague-Dawley rats (6—7 weeks old) were deprived of food but allowed free access to water for 48 h (gastric secretion) or 24 h (aldosterone-like activity) prior to

TABLE III.



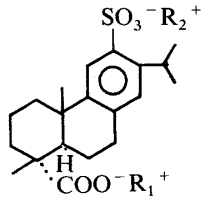
50—61

No.	R_1	R_2	Yield (%)	mp (°C)	Analysis (%) Calcd (Found) C H N	Antisecretory activity % inhibition *i.p.* at 30 mg/kg	Antipepsin activity % inhibition *i.g.* at 100 mg/kg
50	$CH_2NH(CH_2)_2NMe_2$	H	75	>300	$C_{24}H_{40}N_2O_3S \cdot 1/2H_2O$[a] 64.68 9.27 6.29 (64.27 8.94 6.43)	−22	20
51	NHMe	H	46	>300	$C_{20}H_{31}NO_3S$ 65.72 8.55 3.83 (65.48 8.63 3.69)	3	5
52	$CH_2N(CONMe_2)(CH_2)_2NMe_2$	H	47	Amorph. (182)	$C_{27}H_{45}N_3O_4S \cdot H_2O$ 61.68 9.01 7.99 (61.30 8.59 7.95)	−20	11
53	$CH_2N(Me)CSNH(CH_2)_2NMe_2$	H	58	Amorph. (192)	$C_{26}H_{43}N_3O_3S_2 \cdot 1/2H_2O$[a] 58.18 8.64 7.83 (58.19 8.18 7.77)	−22	20

54	$CH_2NHCOCH_2N(n\text{-}Pr)_2$	Na	50	Amorph. (180)	$C_{28}H_{45}N_2NaO_4S \cdot 1/2H_2O$ 59.55 8.75 4.96 (59.25 8.46 4.90)	17	32
55	$CONMe_2$	Na	69	>300	$C_{22}H_{32}NNaO_4S \cdot 1/2H_2O$ 60.32 7.59 3.20 (60.05 7.77 3.14)	2	73
56	$CONHCH(CH_2)_2SMe$ $\vert$ $COONa$	Na	70	>300	$C_{25}H_{35}NNa_2O_6S \cdot 1/2H_2O$ 53.24 6.43 2.48 (52.99 6.49 2.39)	−1	94
57	$CONHCH(CH_2)_2S^+Me_2$ $\vert$ $COOH$	—	72	199 (dec.)	$C_{26}H_{39}NO_6S_2 \cdot H_2O$ 57.43 7.60 2.58 (57.61 7.62 2.60)	8	−3
58	$CONH(CH_2)_2CONH$ $\vert$ $CH_2CHCOONa$ $N \quad NH$	Na	72	260 (dec.)	$C_{29}H_{38}N_4Na_2O_7S \cdot 3H_2O$ 50.72 6.46 8.16 (51.14 6.91 7.62)	7	15
59	$CONH(CH_2)_2CSNH_2$	Na	31	200 (dec.)	$C_{23}H_{33}N_2NaO_4S_2 \cdot H_2O$ 54.52 6.96 5.53 (54.85 6.68 5.56)	−1	−21
60	$CSNHMe$	NH_4	63	>300 (dec.)	$C_{21}H_{34}N_2O_3S_2$ 59.12 8.03 6.57 (59.16 7.79 6.40)	−3	68
61	$CH_2OOC(CH_2)_2COOH$	H	96	Amorph. (135)	$C_{24}H_{34}O_7S \cdot 2H_2O$[a] 57.35 7.62 (57.60 7.52)	15	75

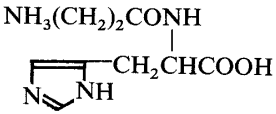
a) These compounds were tested biologically as the sodium salts.

TABLE IV.



62—74

No.	R_1	R_2	Method[a]	Yield (%)	mp (°C)	Analysis (%) Calcd (Found) C	H	N	Antisecretory activity % inhibition *i.p.* at 30 mg/kg	Antipepsin activity % inhibition *i.g.* at 100 mg/kg
62	H	Na	A	90	>300	$C_{20}H_{27}NaO_5S \cdot 5H_2O$			−2	96
						48.82	7.58			
						(49.15	7.65)			
63	Na	Na	A	90	>300	$C_{20}H_{26}Na_2O_5S \cdot H_2O$			34	92
						54.34	6.39			
						(54.63	6.37)			
64	Ca/2	Ca/2	B	46	>300	$C_{20}H_{26}CaO_5S \cdot 5/2H_2O$			5	99
						51.88	6.75			
						(51.66	7.01)			
65	Mg/2	Mg/2	B	63	>300	$C_{20}H_{26}MgO_5S \cdot H_2O$			32	72
						57.19	6.72			
						(57.50	7.12)			

66	Al/3	Al/3	B	60	>300	$C_{20}H_{26}Al_{2/3}O_5S \cdot 7/3H_2O$ 54.62 6.98 (54.99 6.69)	28	95
67	iso-$PrNH_3$	iso-$PrNH_3$	A	82	>300	$C_{26}H_{46}N_2O_5S$ 62.70 9.31 5.63 (62.31 9.12 5.59)	33	95
68	$NH_3(CH_2)_4NH_3$		A	66	284—287 (dec.)	$C_{24}H_{40}N_2O_5S \cdot 1/2H_2O$ 60.43 8.88 5.87 (60.67 8.41 5.66)	10	84
69	H	$NH_2CH(COOH)(CH_2)_4NH_3$	A	87	236 (dec.)	$C_{26}H_{42}N_2O_7S \cdot H_2O$ 57.40 8.15 5.15 (57.44 7.74 4.81)	28	94
70	H	$NH_3CH(COOH)(CH_2)_2CONH_2$	A	59	240 (dec.)	$C_{25}H_{38}N_2O_8S \cdot 1/2H_2O$ 56.12 7.35 5.24 (56.01 7.27 5.46)	28	90
71	H		A	87	222—224 (dec.)	$C_{29}H_{42}N_4O_8S \cdot H_2O$ 55.82 7.11 8.97 (55.45 7.39 9.21)	13	72
72	H	$Me_2S(CH_2)_2CH(NH_2)COOH$	C	93	269 (dec.)	$C_{26}H_{41}NO_7S_2 \cdot 1/2H_2O$ 56.49 7.65 2.53 (56.30 7.81 2.54)	−43	84
73	H	$(C_{16}H_{26}N_2O_2)/2^{b)}$	C	52	265 (dec.)	$C_{28}H_{41}NO_6S$ 64.71 7.95 2.70 (64.29 7.95 2.90)	1	90
74	H	$C_{14}H_{21}N_2O^{c)}$	A	59	216—218 (dec.)	$C_{34}H_{48}N_2O_6S$ 66.64 7.89 4.57 (66.33 7.99 5.00)	29	69

a) See the experimental section. *b*) The formula represents the cationic part of compound **24**. *c*) The formula represents *N*-[2-(dimethylamino)ethyl]-4-phenyl-2-pyrrolidinone.

experiments. The inhibitory activity of a test compound on gastric secretion was expressed as the percent (%) inhibition relative to the control group given the vehicle only. Aldosterone-like activity of the test compound, assessed in terms of the Na/K value, was expressed as percent (%) of the control given the vehicle only.

Gastric Secretion

Under ether anesthesia, the abdomen was opened and the pylorus was ligated.[19] Immediately after the ligation, a test compound suspended or dissolved in distilled water was administered intragastrically (*i.g.*) or intraperitoneally (*i.p.*). The gastric juice was collected 5 h after the administration of the test compound and the volume was measured after centrifugation at 2500 rpm for 10 min. The concentration of pepsin in the gastric juice was determined by Anson's method[20] using hemoglobin as a substrate.

Aldosterone-like Activity

Rats were given orally 30 ml/kg of physiological saline solution. One hour later, 30 ml/kg of suspension or solution of a test compound in physiological saline was given by the oral route. After the administration of the test compound, potassium and sodium concentrations in the urine excreted during a 4 h period were measured by using a flame photometer. Aldosterone-like activity of the compounds was assessed in terms of the Na/K value in the urine.

Results and Discussion

Dehydroabietic acid (**1**) itself was marginally active in the antisecretory test and had no antipepsin activity. However, the compounds (**26**, **27**, **30**, and **35**—**38**) having nitrogen functions derived from the carboxyl group of **1** (Table I) showed high antisecretory activity with very weak or no reduction of pepsin concentration in the gastric juice.

12-Sulfonamide derivatives of dehydroabietic acid (Table II) showed no significant activity in either test except for the sugar derivative (**43**), which showed moderate antipepsin activity. Of the 12-sulfonic acid derivatives bearing an amino, carbamoyl, thiocarbamoyl, ureido, or ester group at the C-4 position (Table III), **55**, **56**, **60**, and **61** exhibited good antipepsin activity comparable or superior to that of carbenoxolone sodium (**23**). However, very high antisecretory and weak antipepsin activities seen in the amino compounds (**30**, **35**, and **37**) (Table I) were almost completely lost in the corresponding 12-sulfonic acid derivatives (**51**, **52**, and **54**).

In a series of salts prepared from 12-sulfodehydroabietic acid (**15**) (Table IV), highly potent antipepsin activity was observed with almost all compounds (**62**—**73**), which were all more active than carbenoxolone sodium (**23**). Thus, the presence of two acidic functional groups, one at each end of the dehydroabietane nucleus, appears to be necessary for the appearance of antipepsin activity. The salt **73**, prepared from **15** and the spiro-ammonium compound (**24**)[17] in the hope of conferring both antisecretory and antipepsin activities, did not exhibit the expected combined effect, but showed only antipepsin activity.

Compounds **62**—**64** were also tested for aldosterone-like action, an unfavorable side effect of carbenoxolone sodium (**23**), by determining the sodium *vs.* potassium ratio in urine after oral administration in rats. As illustrated in Table V, the compounds did not show any significant aldosterone-like activity.

Thus, the replacement of the oleanane skeleton of carbenoxolone sodium (**23**) by the simpler dehydroabietane nucleus eliminated the undesirable side effect of the former and conferred more pronounced antipepsin activity. Among the salts of 12-sulfodehydroabietic acid (**62**—**74**), further investigations of the mono sodium salt (**62**) as an antiulcer agent having cytoprotective properties are in progress. These results will be described in a later

TABLE V

No.	Na/K ratio in urine % of the control	
	p.o. at 500 mg/kg	*p.o.* at 1000 mg/kg
Control	100	100
62	96	101
63	108	115
64	105	96
23[a]	55[b]	

a) Carbenoxolone sodium (**23**) was tested at 50 mg/kg *p.o.* *b*) $P<0.01$.

communication.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded in Nujol mulls on a Hitachi IR-215 spectrometer. Nuclear magnetic resonance (NMR) spectra were taken in $CDCl_3$ or dimethylsulfoxide (DMSO)-d_6 at 60 MHz on a JEOL PMX-60 spectrometer with tetramethylsilane (TMS) as an internal reference. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and br=broad. Mass spectra (MS) were measured with a Hitachi RMU-6M instrument.

***N,N*-Dimethyl-3-(dehydroabietoxy)propylamine (26)**——Sodium hydride (50% mineral oil disp., 0.5 g) was added to a solution of **2** (1 g) in tetrahydrofuran (THF) (15 ml) and dimethylformamide (DMF) (1.5 ml) at room temperature. The mixture was stirred for 15 min, then 3-(chloropropyl)dimethylamine (2.06 g) was added, and the whole was refluxed for 24 h. A small amount of aq. THF was added under ice-cooling, and the solvent was removed *in vacuo* to leave an oily residue, which was diluted with H_2O and extracted with EtOAc. The EtOAc layer was washed with aq. NaCl, dried over Na_2SO_4, and evaporated to leave an oil (1.2 g). Conversion to the citrate and crystallization from Et_2O gave the citrate of **26** (0.82 g). IR ν_{max}^{Nujol} cm^{-1}: 1580, 1110. MS *m/e*: 371 (M^+), NMR ($CDCl_3$) δ: 2.19 (6H, s).

Dehydroabietyl Chloroformate (5)——A solution of **2** (5 g) in THF (20 ml) was added dropwise to a solution of phosgene (4 g) in THF (5 ml) at −15 °C. The mixture was stirred at −5 °C for 1 h and concentrated *in vacuo*. The residue was crystallized from Et_2O to give **5** (5.9 g, quantitative), mp 76—77 °C (dec.), IR ν_{max}^{Nujol} cm^{-1}: 1780, 1500. MS *m/e*: 350, 348 (M^+).

Dehydroabietyl *N*-[2-(Dimethylamino)ethyl]carbamate (27)——A solution of **5** (1 g) in Et_2O (5 ml) was added dropwise to a solution of 2-(dimethylamino)ethylamine (1 ml) in THF (4 ml) at 0 °C. After being stirred at 0—5 °C for 15 min and then at room temperature for 1 h, the mixture was diluted with H_2O and extracted with Et_2O. The Et_2O extracts were washed with aq. NaCl, dried over Na_2SO_4, and concentrated. The residue was converted to the oxalate and recrystallized from Me_2CO to give the oxalate of **27** (0.68 g), IR ν_{max}^{Nujol} cm^{-1}: 3300, 1730. MS *m/e*: 400 (M^+).

Compounds **28** and **29** were prepared in a similar manner (Table I).

18-Nordehydroabietyl Isocyanate (4)——A mixture of **1** (15 g), Et_3N (5.35 g), DPPA (14 g), and dioxane (150 ml) was heated under reflux for 3 h. Removal of the solvent *in vacuo* gave an oil which was purified by chromatography (SiO_2, hexane–benzene, 5:1). Compound **4** was obtained as a colorless oil (13.4 g, 90%), IR $\nu_{max}^{liq.}$ cm^{-1}: 2250. MS *m/e*: 297 (M^+).

***N*-Methyl-18-nordehydroabietylamine Hydrochloride (30)**——A solution of **4** (13.4 g) in Et_2O (150 ml) was added dropwise to a mixture of LAH (10.8 g) in Et_2O (100 ml) below 34 °C. The mixture was refluxed for 12 h, decomposed by addition of aq. THF, and filtered. The filtrate was concentrated to leave a viscous oil (11.7 g), which was treated with 30% HCl in EtOH. Removal of the solvent gave **30** as a crystalline powder (14.3 g, 98%), mp 196—199 °C [lit.[10] mp 199—202 °C]. IR ν_{max}^{Nujol} cm^{-1}: 2750, 2440, 1590, 1130. MS *m/e*: 285 (M^+), 270, 242.

***N*-(18-Nordehydroabietyl)-4-morpholinecarboxamide (31)**——A mixture of **1** (1 g), DPPA (1.3 g), Et_3N (0.5 g), and dioxane (12 ml) was refluxed for 2 h, and then morpholine (0.5 ml) was added thereto. After heating of the mixture for 1.5 h, the solvent was removed *in vacuo* to leave an oil, which was dissolved in benzene. The benzene solution was washed successively with aq. Na_2CO_3 and H_2O and dried over Na_2SO_4. Removal of the solvent afforded an oily material (1.2 g) which was purified by chromatography (SiO_2) and crystallized from Me_2CO to give **31** (0.82 g). IR ν_{max}^{Nujol} cm^{-1}: 3360, 1625, 1540, 1500. MS *m/e*: 384 (M^+). NMR ($CDCl_3$) δ: 3.19 (4H, q, $J_1=4.5$ Hz, $J_2=6$ Hz), 3.60 (4H, q, $J_1=4.5$ Hz, $J_2=6$ Hz).

In a similar manner, compounds **32** and **33** were obtained (Table I).

***N*-[2-(Dimethylamino)ethyl]dehydroabietamide (34)**——A solution of **3** (1 g) in THF (2 ml) was added dropwise to an ice-cooled mixture of 2-(dimethylamino)ethylamine (0.72 g), K_2CO_3 (1 g), and aq. THF (7 ml). The mixture was

stirred at room temperature for 3 h, then the solvent was removed *in vacuo*, and the residue was diluted with H_2O and extracted with EtOAc. The EtOAc solution was washed successively with H_2O, aq. $NaHCO_3$, and aq. NaCl and dried over Na_2SO_4. Evaporation of the solvent gave an oily residue, which was treated with EtOH–HCl to give the hydrochloride of **34** (0.8 g) as hygroscopic needles. IR ν_{max}^{Nujol} cm^{-1}: 1640. MS *m/e*: 370 (M^+).

***N*-[2-(Dimethylamino)ethyl]dehydroabietylamine (8)**——A solution of **34** (free base, 13 g) in THF (130 ml) was added to an ice-cooled mixture of LAH (6 g) and THF (100 ml). The mixture was refluxed for 12 h and worked up in the usual manner. The product was converted to the hydrochloride and recrystallized from MeOH–EtOAc to give the dihydrochloride of **8** (7.1 g, 47%), mp 251—252 °C. IR ν_{max}^{Nujol} cm^{-1}: 3400, 2750—2400 (br). MS *m/e*: 356 (M^+).

***N*-(Dehydroabietyl)-*N*-[2-(dimethylamino)ethyl]-*N'*,*N'*-dimethylurea (35)**——This compound was prepared from **8** and *N*,*N*-dimethylcarbamoyl chloride in the manner described above (Table I). IR ν_{max}^{Nujol} cm^{-1}: 1640. MS *m/e*: 427 (M^+).

***N*-(Dehydroabietyl)-*N*-methyl-*N'*-[2-(dimethylamino)ethyl]-thiourea (36)**——A mixture of *N*-methyldehydroabietylamine (**7**) (0.42 g), 2-(dimethylamino)ethyl isothiocyanate[13] (0.2 g), and EtOH (10 ml) was refluxed for 2 h and concentrated *in vacuo* to leave an oil. An ethereal solution of this oil was treated with MeOH–HCl to give the hydrochloride of **36** (0.6 g). IR ν_{max}^{Nujol} cm^{-1}: 3260, 1520. MS *m/e*: 429 (M^+). NMR ($CDCl_3$) δ: 2.84 (6H, s), 3.31 (3H, s).

2-Chloro-*N*-(dehydroabietyl)acetamide (9)——A solution of dehydroabietylamine (**6**) (10.1 g) in THF (20 ml) was added dropwise to a cold mixture of chloroacetyl chloride[14] (4.26 g), Na_2CO_3 (10 g), and THF (20 ml) over a period of 30 min. After being stirred at room temperature for 12 h, the mixture was diluted with aq. $NaHCO_3$, concentrated, and extracted with Et_2O. The Et_2O solution was washed successively with dilute HCl, 10% NaOH, and aq. NaCl and dried over Na_2SO_4. Evaporation of the solvent gave an oil of **9** (10.7 g, 80%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430, 1670. MS *m/e*: 363, 361 (M^+). NMR ($CDCl_3$) δ: 3.22 (2H, d, J=6.2 Hz), 4.03 (2H, s).

***N*-(Dehydroabietyl)-2-(dipropylamino)acetamide (37)**——A mixture of **9** (1.0 g), dipropylamine (0.3 g), Na_2CO_3 (0.5 g), and THF (10 ml) was refluxed for 2 h and concentrated. The residue was taken up in H_2O and Et_2O. The Et_2O layer was washed with 10% NaOH and aq. NaCl, dried over Na_2SO_4, and concentrated. The residue was treated with maleic acid in Et_2O and recrystallized from Me_2CO and Et_2O to give the maleate of **37** (1.21 g). IR ν_{max}^{Nujol} cm^{-1}: 1680. MS *m/e*: 426 (M^+). Compounds **38** and **39** were prepared in a similar manner (Table I).

12-(Chlorosulfonyl)dehydroabietic Acid (16)——PCl_5 (5 g) was added to a mixture of **62** (4.7 g, dried over P_2O_5 at 50 °C *in vacuo* for 12 h) and 1,2-dichloroethane (50 ml) during 30 min. After the mixture had been refluxed for 2 h, insoluble materials were filtered off, and the filtrate was concentrated *in vacuo*. The residue was dissolved in aq. THF (6 : 1, 40 ml) and the solution was stirred at room temperature for 12 h. THF was removed, and the aqueous mixture was extracted with Et_2O. The Et_2O layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was recrystallized from hexane–benzene to give **16** (3.3 g, 71%), mp 226—227 °C. IR ν_{max}^{Nujol} cm^{-1}: 1690. MS *m/e*: 400, 398 (M^+). *Anal.* Calcd for $C_{20}H_{27}ClO_4S$: C, 60.35; H, 6.84; Cl, 8.91; S, 8.06. Found: C, 60.41; H, 6.96; Cl, 9.08; S, 7.80.

12-Sulfamoyldehydroabietic Acid (40)——A solution of **16** (1.1 g) in THF (12 ml) was added dropwise to cold conc. aq. NH_3 (6 ml). The mixture was allowed to stand at room temperature for 12 h, then diluted with H_2O. The precipitated solid was collected and recrystallized from aq. MeOH to give **40** (0.75 g). IR ν_{max}^{Nujol} cm^{-1}: 3350, 3250, 1710. MS *m/e*: 379 (M^+).

12-[[2-(Dimethylamino)ethyl]sulfamoyl]dehydroabietic Acid (41)——A solution of **16** (2.4 g) in THF (20 ml) was added dropwise to a cold solution of 2-(dimethylamino)ethylamine (0.9 g) in H_2O (8 ml). Aq. THF (1 : 1, 120 ml) was added to the mixture, and stirring was continued at room temperature for 3 h. The mixture was concentrated, then diluted with 10% HCl. The precipitate was filtered off and recrystallized from MeOH to give **41** (1 g). IR ν_{max}^{Nujol} cm^{-1}: 1720, 1690. MS *m/e*: 450 (M^+).

12-[(2-Aminoethyl)sulfamoyl]dehydroabietic Acid (42)——A solution of **16** (1.2 g) in THF (8 ml) was added to a cold mixture of ethylenediamine (1.3 g), Et_3N (2 ml), and H_2O (8 ml). After being stirred for 3 h at room temperature, the mixture was concentrated, and the residue was dissolved in 10% NaOH. The alkaline solution was neutralized with conc. HCl, and the precipitate was filtered off and dried to give **42** (0.66 g). IR ν_{max}^{Nujol} cm^{-1}: 1620. MS *m/e*: 422.

12-[(2-Deoxy-2-glucosyl)sulfamoyl]dehydroabietic Acid (43)——This compound was prepared in the same manner as described for **42**. The crude product was purified by chromatography (SiO_2, $CHCl_3$: MeOH = 9 : 1) to give **43**. IR ν_{max}^{Nujol} cm^{-1}: 3350, 1685, 1130, 1050.

12-[[2-(*N'*-Methylthioureido)ethyl]sulfamoyl]dehydroabietic Acid (44)——A mixture of **42** (1.27 g), 1 N NaOH (2.9 ml), methyl isothiocyanate (0.68 g), H_2O (200 ml), and THF (200 ml) was warmed to form a homogeneous solution, then allowed to stand at room temperature for 12 h. The THF was removed, then the mixture was acidified with 10% HCl. The precipitate was collected by filtration, washed with H_2O, and recrystallized from aq. MeOH to give **44** (1 g). IR ν_{max}^{Nujol} cm^{-1}: 3370, 1720, 1140, 1125. MS *m/e*: 495 (M^+).

12-[[*N'*-[2-(Dimethylamino)ethyl]thioureido]sulfonyl]dehydroabietic Acid (45)——A mixture of **40** (1.14 g), 1 N NaOH (5.83 ml), dimethylaminoethyl isothiocyanate (1 g), and 90% aq. Me_2CO (16 ml) was heated at 60 °C for 4 d. Concentration and neutralization with 10% HCl precipitated a solid which was collected by filtration, purified by chromatography (SiO_2, $CHCl_3$: MeOH = 10 : 1) and recrystallized from MeOH to give **45** (0.6 g). IR ν_{max}^{Nujol} cm^{-1}: 3200, 1720, 1535, 1315.

12-[(2-Carboxyethyl)sulfamoyl]dehydroabietic Acid (46)——A mixture of **16** (2 g), β-alanine (4.45 g), $NaHCO_3$ (4.2 g), H_2O (40 ml), and THF (30 ml) was stirred at room temperature for 6 h. The THF was removed, then the residue was acidified with dil. HCl (pH = 3) and extracted with EtOAc. The EtOAc layer was washed with aq. NaCl, dried over Na_2SO_4, and evaporated. The residue was recrystallized from aq. MeOH to give **46** (1.0 g). IR ν_{max}^{Nujol} cm^{-1}: 3400, 1690. MS *m/e*: 451 (M^+).

In a similar manner, **47**, **48**, and **49** were obtained (Table II).

***N*-[2-(Dimethylamino)ethyl]-12-sulfodehydroabietylamine (50)**——Compound **8** (H_2SO_4 salt, 2.8 g) was added in small portions to conc. H_2SO_4 (28 ml) with stirring at −5 °C over a period of 30 min. After being stirred for 3 h at room temperature, the mixture was poured onto ice sticks and the resultant solid was filtered off, washed with cold H_2O, and dissolved in aq. EtOH. The solution was made alkaline (pH = 9) with 30% NaOH and washed with Et_2O. Concentration and cooling of the aqueous layer deposited the sodium salt of **50** (2.62 g, 93%) as a solid, mp 300 °C. IR ν_{max}^{Nujol} cm^{-1}: 3450, 1180. *Anal.* Calcd for $C_{24}H_{39}N_2NaO_3 \cdot H_2O$: C, 60.48; H, 8.67; N, 5.88; S, 6.73. Found: C, 60.87; H, 8.52; N, 5.87; S, 6.93. When the aqueous layer described above was neutralized with aq. HCl, crystalline **50** (free acid, 2.04 g) was obtained. IR ν_{max}^{Nujol} cm^{-1}: 3000—2400 (br), 1220, 1145. Compounds **51**, **54**, and **55** were prepared in a similar manner (Table III).

***N*-[2-(Dimethylamino)ethyl]-*N*-12-sulfodehydroabietyl-*N'*,*N'*-dimethylurea (52)**——Cold conc. H_2SO_4 (11.3 ml) was slowly added to **35** (H_2SO_4 salt, 1.13 g) with stirring under ice-cooling. The mixture was worked up as described for **50** to give **52** (0.65 g) as an amorphous solid. IR ν_{max}^{Nujol} cm^{-1}: 3440, 1640, 1210, 1155. Compound **53** was prepared similarly (Table III).

***N*-(Dehydroabietoyl)methionine (11)**——A solution of **3** (16.9 g) in THF (40 ml) and a solution of Na_2CO_3 (5.64 g) in H_2O (40 ml) were added dropwise alternately to an ice-cooled solution of methionine (7.94 g) in aq. Na_2CO_3 (2.82 g, 104 ml) with stirring over 3 h, and THF (120 ml) was added thereto to dissolve the precipitate. After being stirred for 12 h at room temperature, the mixture was concentrated, acidified with 10% HCl, and extracted with EtOAc. The EtOAc solution was washed with aq. NaCl, dried over Na_2SO_4, and concentrated. The residual solid was recrystallized from EtOAc–MeOH to give **11** (14.2 g, 62%), mp 190—192 °C. IR ν_{max}^{Nujol} cm^{-1}: 3380, 1730, 1620, 1530. MS *m/e*: 431 (M^+), 416. *Anal.* Calcd for $C_{25}H_{37}NO_3S$: C, 69.66; H, 8.65; N, 3.25. Found: C, 70.06; H, 8.78; N, 3.47.

***N*-(12-Sulfodehydroabietoyl)methionine Disodium Salt (56)**——Compound **11** (3.2 g) was sulfonated in the same manner as described for **50**, and the resultant alkaline solution (pH 9) was concentrated to dryness. The residue was extracted with EtOH. Concentration of the EtOH solution yielded crystals, which were collected by filtration and dried to give **56** (2.9 g). IR ν_{max}^{Nujol} cm^{-1}: 3440, 1620, 1590, 1580, 1510.

***N*-(12-Sulfodehydroabietoyl)-*S*-methylmethioninesulfonium Inner Salt (57)**——A mixture of **56** (4.6 g), methyl iodide (3 ml), 85% HCOOH (18 ml), and AcOH (8 ml) was stirred in the dark at room temperature for 3 d. After evaporation of the solvent, the residue was dissolved in warm aq. EtOH, and the solution was allowed to stand in a refrigerator overnight. The precipitated solid was filtered off, washed with cold EtOH, and recrystallized from aq. Me_2CO (1 : 3, 200 ml) to give **57** as fine needles (3.5 g). IR ν_{max}^{Nujol} cm^{-1}: 3400 (br), 1720, 1620, 1510.

Methyl *N*-(Dehydroabietoyl)carnocinate (12)——A solution of **3** (4.78 g) in THF (20 ml) was added dropwise with stirring to an ice-cooled mixture of methyl carnocinate (2 HCl salt, 7.05 g), Et_3N (9.11 g), and DMF (40 ml) over a period of 50 min, and the whole was stirred under ice-cooling for 1 h. After being stirred at room temperature for 18 h, the mixture was concentrated. The residue was diluted with H_2O, and the solution was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with aq. NaCl and dried over Na_2SO_4. Evaporation of the solvent gave a pale yellow liquid (10 g), which was purified by chromatography (SiO_2, $CHCl_3$: MeOH = 10 : 1) to give **12** as an amorphous powder (2.37 g, 30%). IR ν_{max}^{Nujol} cm^{-1}: 3350—3200 (br), 1735, 1630, 1510. MS *m/e*: 522 (M^+). NMR ($CDCl_3$) δ: 3.66 (3H, s).

***N*-(12-Sulfodehydroabietoyl)carnosine (58)**——Compound **12** (2.3 g) was sulfonated in the same manner as described for **52** to give **17** (2.92 g), mp 262—265 °C (dec.). A solution of NaOH (0.55 g) in H_2O (10 ml) was added dropwise to a mixture of **17** (2.9 g) and EtOH (10 ml) with stirring. After being stirred at room temperature for 2 h, the mixture was concentrated *in vacuo*. The residue was diluted with H_2O, then the solution was washed with Et_2O, and acidified with 10% HCl (pH = 2) to give **58** (free acid, 1.99 g, 72%), mp 245 °C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3400 (br), 1730, 1660, 1620, 1575, 1540. NMR (DMSO-d_6) δ: 6.87 (1H, s), 7.37 (1H, s), 7.65 (1H, s), 8.97 (1H, s). Elemental analysis values for the disodium salt are given in Table III.

12-(Methoxysulfonyl)dehydroabietic Acid (18)——A solution of NaOH (11 g) in H_2O (100 ml) was added dropwise to a solution of **16** (40 g) in MeOH (1500 ml) at 5 °C over a period of 20 min. After being stirred for 20 min, the mixture was acidified with 10% HCl, and concentrated *in vacuo*. The residue was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with aq. NaCl, dried over Na_2SO_4, and evaporated to give **18** (32 g, 80%) as an amorphous powder. IR ν_{max}^{Nujol} cm^{-1}: 1690, 1190, 1170. MS *m/e*: 394 (M^+). NMR ($CDCl_3$ + DMSO-d_6) δ: 3.7 (3H, s), 7.2 and 7.8 (each 1H, s).

***N*-Methyl-12-(methoxysulfonyl)dehydroabietamide (19)**——A mixture of **18** (5.0 g) and $SOCl_2$ (10 ml) was refluxed for 1 h, then evaporated. The residue was dissolved in THF (20 ml), and aq. $MeNH_2$ (30%, 4 ml) was added to the resulting solution under cooling. The mixture was acidified with 10% HCl and concentrated. The solid that separated was filtered off, washed with H_2O and then with MeOH, dried, and recrystallized from MeOH to give **19**

(2.7 g, 52%), mp 147—148 °C. IR ν_{max}^{Nujol} cm^{-1}: 1655. MS *m/e*: 407 (M^+), 392, 333. NMR ($CDCl_3$) δ: 2.83 (3H, d, J= 6 Hz), 3.70 (3H, s). *Anal.* Calcd for $C_{22}H_{33}NO_4S \cdot 1/2CH_3OH$: C, 63.80; H, 8.33; N, 3.31. Found: C, 63.78; H. 8.18; N, 3.32.

***N*-Methyl-12-(methoxysulfonyl)dehydrothioabietamide (20)**——A mixture of **19** (4.0 g), P_2S_5 (2.2 g), K_2S (1.44 g), and benzene (50 ml) was stirred at 70 °C for 2.5 h. Insoluble material was removed by filtration, and the filtrate was concentrated to give a solid, which was chromatographed and recrystallized from benzene to give **20** (2.5 g, 60%), mp 185—187 °C. IR ν_{max}^{Nujol} cm^{-1}: 3360, 1530. MS *m/e*: 423 (M^+), 390. NMR ($CDCl_3$) δ: 3.3 (3H, d, J=4.5 Hz), 3.7 (3H, s). *Anal.* Calcd for $C_{22}H_{33}NO_3S_2 \cdot 1/2C_6H_6$: C, 64.90; H, 7.84; N, 3.03. Found: C, 64.94; H, 7.65; N, 2.78.

***N*-Methyl-12-sulfodehydrothioabietamide Ammonium Salt (60)**——A mixture of **20** (1.46 g), conc. aq. NH_3 (45 ml), and THF (180 ml) was refluxed for 3.5 h, then concentrated, and neutralized with 10% HCl. The resulting precipitate was filtered off and recrystallized from aq. MeOH to give **60** (0.9 g). IR ν_{max}^{Nujol} cm^{-1}: 3350, 1520. MS *m/e*: 409 (M^+).

***N*-(2-Cyanoethyl)dehydroabietamide (13)**——2-Cyanoethylamine (1.9 g) was acylated in the same manner as described for **12** to give **13** (4.5 g, 96%), mp 139—141 °C (recrystallized from hexane–benzene). IR ν_{max}^{Nujol} cm^{-1}: 3350, 2250, 1635. MS *m/e*: 352 (M^+), 337.

***N*-[2-(Thiocarbamoyl)ethyl]dehydroabietamide (14)**——A mixture of **13** (3.53 g), *O,O'*-diethyl dithiophosphate[16] (2.1 g), benzene (5 ml), and THF (3 ml) was stirred for 1 h at room temperature. HCl gas was bubbled into the mixture at room temperature for 30 min and then at 50 °C for 30 min. Additional *O,O'*-diethyl dithiophosphate (1.9 g) was added to the reaction mixture, and bubbling of HCl gas was continued for 30 min at 50 °C. The mixture was then evaporated *in vacuo*. The oily residue was diluted with 5% aq. Na_2CO_3 and extracted with benzene. The benzene solution was washed with aq. NaCl, dried over Na_2SO_4, and concentrated to give **14** as needles (1.9 g, 49%), mp 153—155 °C. IR ν_{max}^{Nujol} cm^{-1}: 3300, 1680. MS *m/e*: 386 (M^+), 352, 255. *Anal.* Calcd for $C_{23}H_{24}N_2OS$: C, 71.46; H, 8.86; N, 7.25; S, 8.29. Found: C, 71.42; H, 8.66; N, 7.17; S, 8.24.

***N*-[2-(Thiocarbamoyl)ethyl]-12-sulfodehydroabietamide (59)**——In the same manner as described for **50**, **14** was sulfonated to give **59**. IR ν_{max}^{Nujol} cm^{-1}: 3400 (br), 1630, 1190.

12-Sulfodehydroabietyl Alcohol (21)——A solution of **15** (8.14 g) in THF (25 ml) was added dropwise with stirring to a mixture of LAH (3.0 g) in THF (40 ml) at 10 °C, and the mixture was stirred at room temperature for 12 h. The mixture was decomposed by addition of H_2O and acidified with 10% HCl. The organic layer was separated, and the aqueous layer was extracted with THF. The combined THF solutions were dried over Na_2SO_4 and evaporated to dryness. The residual solid was recrystallized from EtOAc–MeOH to give **21** (4.6 g, 54%), mp 198 °C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3250, 1140. MS *m/e*: 366 (M^+), 333. *Anal.* Calcd for $C_{20}H_{30}O_4S \cdot 2H_2O$: C, 59.67; H, 8.51. Found: C, 59.89; H, 8.23.

12-Sulfodehydroabietyl Hydrogen Succinate (61)——A mixture of **21** (2.04 g), succinic anhydride (3.0 g), and pyridine (30 ml) was refluxed for 7 h and concentrated to dryness. The residual solid was washed with Et_2O and dissolved in H_2O. The solution was acidified with 10% HCl, and the separated solid was filtered off and recrystallized from EtOAc–MeOH to give **61** (2.45 g). IR ν_{max}^{Nujol} cm^{-1}: 3270, 1730, 1700.

Preparation of the Salts of 12-Sulfodehydroabietic Acid (15) Method A——12-sulfodehydroabietic Acid Disodium Salt (**63**): NaOH (2.1 g) was added to a mixture of **15** (10 g) and H_2O (50 ml), and the solution was treated with charcoal, then filtered. The filtrate was concentrated to a small volume (20 ml) *in vacuo* and heated to dissolve the separated solid. After cooling, the deposited crystals were filtered off and dried in air to give the disodium salt (**63**) (10.4 g), which contained 8.5 mol of H_2O. $[\alpha]_D^{20}$: +48.2° (c=2.5, H_2O). IR ν_{max}^{Nujol} cm^{-1}: 3480 (br), 1540, 1461. When this hydrate was dried under reduced pressure (3 mmHg) over P_2O_5 at 160 °C for 17 h, the anhydrous salt was obtained; it gradually absorbed atmospheric moisture to give the monohydrate of **63**.

12-Sulfodehydroabietic Acid 12-Sodium Salt Pentahydrate (**62**): This compound was prepared either by method A or by the method described below. A solution of **63** (5 g) in H_2O (50 ml) was adjusted to pH 3.7 with 1 N HCl, and the precipitated solid was filtered off. The solid was dried in air and recrystallized from H_2O to give **62** (3.87 g), $[\alpha]_D^{20}$: +59.4° (c=0.5, H_2O). IR ν_{max}^{Nujol} cm^{-1}: 3500—3400 (br), 1689, 1461, 1380.

Method B——12-Sulfodehydroabietic Acid Calcium Salt (**64**): A solution of $CaCl_2$ (1.5 g) in H_2O (10 ml) was added to a solution of **63** (5 g) in H_2O (20 ml). The precipitated solid was collected by filtration and recrystallized from aq. MeOH to give **64** (2.5 g). IR ν_{max}^{Nujol} cm^{-1}: 3550—3350 (br), 1543, 1400.

Method C——12-Sulfodehydroabietic Acid *S*-Methylmethioninesulfonium Salt (**72**): A solution of *S*-methylmethioninesulfonium iodide[15] (1.16 g) in H_2O (10 ml) was added to a solution of 12-sulfodehydroabietic acid silver salt [prepared from **15** (1.52 g) and Ag_2CO_3 (0.55 g)] in H_2O (300 ml). The mixture was diluted with EtOH (400 ml), and the precipitate was filtered off. The filtrate was concentrated to dryness, and the residue was exracted with 50% aq. EtOH. The aq. EtOH solution was concentrated to a small volume (20 ml), then the concentrate was diluted with Me_2CO (400 ml), and left at room temperature overnight. The precipitate was collected by filtration and dried over P_2O_5 *in vacuo* below 50 °C to give **72** (2.05 g), $[\alpha]_D^{20}$: +57° (c=1, H_2O). IR ν_{max}^{Nujol} cm^{-1}: 3430, 3320, 1680, 1620.

3-(3,4-Dihydroxyphenyl)-8,8-dimethyl-1,8-diazoniaspiro[4,5]decane Dibromide (24)——A solution of **25** (5 g) in hydrobromic acid (48%, 40 ml) was heated under reflux for 4 h, then evaporated to dryness *in vacuo*. The residual

solid was recrystallized from MeOH to give **24** (3.4 g, 70%), mp 278—280 °C. IR ν_{max}^{Nujol} cm^{-1}: 3540—3200 (br), 1600, 1530. *Anal.* Calcd for $C_{16}H_{26}Br_2N_2O_2 \cdot H_2O$: C, 42.14; H, 6.19; Br, 35.09; N, 6.14. Found: C, 41.94; H, 6.16; Br, 34.73; N, 6.04.

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8) IUPAC nomenclature: [1*R*-(1α, 4a*β*, 10aα)]-1,2,3,4,4a,9,10,10a-octahydro-1,4a-dimethyl-7-(1-methylethyl)-1-phenanthrenecarboxylic acid. The term "dehydroabietic acid" has been used for this compound with the numbering depicted in Chart 1. For convenience, the compounds prepared in this study are named as derivatives of dehydroabietic acid. See reference 6.
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