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## New Hypocholesterolemic Abietamide Derivatives. I. Structure-activity Relationship

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Various amides of tetrahydroabietic,  $\Delta^8$ -dihydroabietic, abietic and dehydroabietic acids were prepared and tested for hypocholesterolemic activity in cholesterol-fed rats.

The introduction of an aromatic ring into the amine moiety of secondary amides markedly enhanced the activity of the parent acids. The secondary amides having an aliphatic ring were slightly less active than those having an aromatic ring, but those having an alkyl or allyl group were completely inactive. Tetrahydroabietic and dihydroabietic acids appear to be preferable (in terms of activity) to abietic or dehydroabietic acid as the acid moiety of these amide derivatives.

N-Phenyltetrahydro (18)- or N-phenyl- $\Delta^8$ -dihydroabietamide (19) and N-benzyltetrahydro (20)- or N-benzyl- $\Delta^8$ -dihydroabietamide (21) are considered to be promising parent compounds for potent hypocholesterolemic drugs. In the case of benzyl derivatives of  $\Delta^8$ -dihydroabietamide, N-(4-methoxybenzyl)- $\Delta^8$ -dihydroabietamide (49) and N-( $\alpha$ -benzylbenzyl)- $\Delta^8$ -dihydroabietamide (58) were the most active, being more than 10 times as potent as the corresponding parent compounds.

**Keywords**—serum cholesterol; cholesterol-lowering effect; rat; abietamide derivatives;  $\Delta^8$ -dihydroabietamide derivatives

Since elevated blood lipid levels are important risk factors in the development of atherosclerosis, a new effective and well-tolerated anti-lipemic drug is always a valuable addition to the existing therapeutic means.

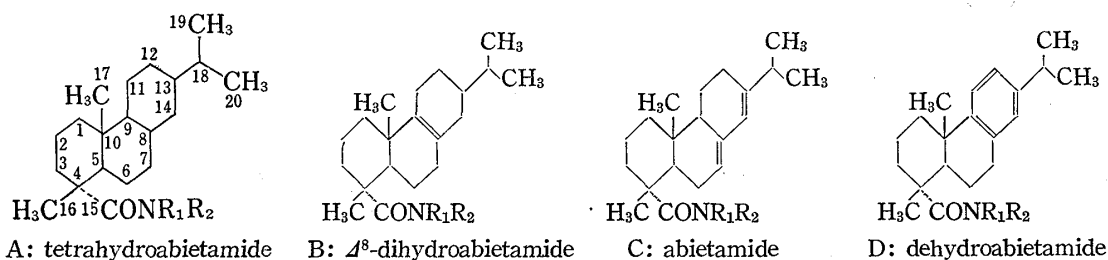
In our previous report<sup>2)</sup> it was found that tricyclic diterpenoids such as totarol, abietic acid, dihydroabietic acid, dehydroabietic acid and their derivatives have serum cholesterol-lowering effects in cholesterol-fed rats. It was further found that certain amide derivatives showed stronger hypocholesterolemic activity than their parent acids. This paper deals with the syntheses of various amide derivatives and their cholesterol-lowering action. Table I shows the hypocholesterolemic activities of abietamide derivatives.

The primary amides of tetrahydroabietic and  $\Delta^8$ -dihydroabietic acids (1, 2) did not retain the cholesterol-lowering activity of their parent acids. As for the secondary amides, introduction of an aliphatic chain into the amine moiety did not reduce or even increased serum cholesterol levels, while a significant improvement of the activity was obtained by the introduction of alicyclic rings, except for compound 14. The presence of aromatic rings in the amine moiety of the secondary amides greatly increased the hypocholesterolemic potency, as exemplified by 18—21 and 23—28. This tendency was more significant in tetrahydroabietamide and  $\Delta^8$ -dihydroabietamide derivatives than in abietamide or dehydroabietamide derivatives, the order of activity being phenyl (19) benzyl (21) phenethyl (23); the differences were particularly marked in  $\Delta^8$ -dihydroabietamide derivatives. In contrast to the secondary amides, however, such an enhancing effect of aromatic residues was not observed in the tertiary

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TABLE I. Hypocholesterolemic Activity of Abietamide



No.	Structure	R <sub>1</sub> R <sub>2</sub>		Formula	Method	Yield (%)	mp (°C)	IR $\nu_{\max}$ (cm <sup>-1</sup> ); CONR <sub>1</sub> R <sub>2</sub>	Recrystn. Solvent	Hypocholesterolemic Activity (% Inhibition)*
1	A	H	H	C <sub>20</sub> H <sub>35</sub> NO	I	81	170—172	1650	Ethylacetate	-9
2	B	H	H	C <sub>20</sub> H <sub>35</sub> NO	I	65	164—166	1650	Ethylacetate	-16
3	B	H	Methyl	C <sub>21</sub> H <sub>35</sub> NO	I	73	141—143	1640	Methanol	-57 <sup>b)</sup>
4	A	H	iso-Propyl	C <sub>23</sub> H <sub>41</sub> NO	I	50	114—116	1630	Isopropanol	15
5	B	H	iso-Propyl	C <sub>23</sub> H <sub>39</sub> NO	I	86	162—163	1621	<i>n</i> -Hexane	-12
6	B	H	Allyl	C <sub>23</sub> H <sub>37</sub> NO	I	76	92—94	1630	Methanol	-16
7	C	H	Allyl	C <sub>23</sub> H <sub>35</sub> NO	II	88	(Glassy)	1650	—	-1
8	B	H	<i>tert</i> -Butyl	C <sub>24</sub> H <sub>41</sub> NO	I	77	145—146	1635	<i>n</i> -Hexane	13
9	C	H	<i>n</i> -Decyl	C <sub>30</sub> H <sub>50</sub> NO	II	50	(Oily)	1640	—	-6
10	C	H	<i>n</i> -Dodecyl	C <sub>32</sub> H <sub>54</sub> NO	II	94	(Oily)	1650	—	3
11	A	H	Cyclopentyl	C <sub>25</sub> H <sub>43</sub> NO	I	92	181—183	1630	Ethanol	22
12	C	H	Cyclopentyl	C <sub>25</sub> H <sub>39</sub> NO	II	81	164—165	1620	Methanol	31 <sup>b)</sup>
13	A	H	Cyclohexyl	C <sub>26</sub> H <sub>45</sub> NO	I	74	146—147	1626	Ethylacetate	48 <sup>b)</sup>
14	D	H	Cyclohexyl	C <sub>26</sub> H <sub>39</sub> NO	I	83	188—189	1620	Methanol	1
15	B	H	Cycloheptyl	C <sub>27</sub> H <sub>45</sub> NO	I	85	176—178	1620	Ethanol	59 <sup>b)</sup>
16	C	H	Cycloheptyl	C <sub>27</sub> H <sub>43</sub> NO	II	95	148	1620	Ethanol	45 <sup>b)</sup>
17	B	H	Adamantyl	C <sub>30</sub> H <sub>47</sub> NO	I	28	180—182	1630	Acetone	31
18	A	H	Phenyl	C <sub>26</sub> H <sub>39</sub> NO	I	79	138—141	1667	Ethanol	86 <sup>b)</sup>
19	B	H	Phenyl	C <sub>26</sub> H <sub>37</sub> NO	I	67	105—107	1640	Ethanol	97 <sup>b)</sup>
20	A	H	Benzyl	C <sub>27</sub> H <sub>41</sub> NO	I	76	112—114	1640	<i>n</i> -Hexane	96 <sup>b)</sup>
21	B	H	Benzyl	C <sub>27</sub> H <sub>39</sub> NO	I	83	125—126	1630	Methanol	64 <sup>b)</sup>
22	C	H	Benzyl	C <sub>27</sub> H <sub>37</sub> NO	II	87	106—107	1630	<i>n</i> -Hexane	36 <sup>a)</sup>
23	B	H	Phenethyl	C <sub>28</sub> H <sub>41</sub> NO	I	33	(Oily)	1623	—	49 <sup>b)</sup>
24	A	H	$\alpha$ -Methylbenzyl	C <sub>28</sub> H <sub>45</sub> NO	I	59	55—60	1635	Ether	79 <sup>b)</sup>
25	B	H	$\alpha$ -Methylbenzyl	C <sub>28</sub> H <sub>41</sub> NO	I	91	125—128	1620	Methanol	93 <sup>b)</sup>
26	C	H	$\alpha$ -Methylbenzyl	C <sub>28</sub> H <sub>39</sub> NO	II	88	83—87	1620	Ether	58 <sup>b)</sup>
27	D	H	$\alpha$ -Methylbenzyl	C <sub>28</sub> H <sub>37</sub> NO	I	71	176—178	1628	Methanol	66 <sup>b)</sup>
28	D	H	$\alpha$ -Ethylbenzyl	C <sub>29</sub> H <sub>39</sub> NO	I	74	153—154	1630	Methanol	66 <sup>b)</sup>
29	A	Methyl	Methyl	C <sub>22</sub> H <sub>39</sub> NO	I	88	(Oily)	1635	—	0
30	B	Methyl	Methyl	C <sub>22</sub> H <sub>37</sub> NO	I	68	74—75	1630	Methanol	-13
31	C	Methyl	Methyl	C <sub>22</sub> H <sub>35</sub> NO	II	73	(Oily)	1600	—	-4
32	A	Methyl	Cyclohexyl	C <sub>27</sub> H <sub>47</sub> NO	I	75	(Oily)	1600	—	15
33	C	Methyl	Cyclohexyl	C <sub>27</sub> H <sub>43</sub> NO	II	76	130—132	1610	Acetone	1
34	C	Allyl	Allyl	C <sub>26</sub> H <sub>41</sub> NO	II	69	(Oily)	1620	—	5
35	A	Methyl	Phenyl	C <sub>27</sub> H <sub>41</sub> NO	I	67	105—107	1640	Ethanol	38 <sup>b)</sup>
36	B	Methyl	Phenyl	C <sub>27</sub> H <sub>39</sub> NO	I	50	119	1630	Methanol	27 <sup>a)</sup>
37	D	Methyl	Phenyl	C <sub>27</sub> H <sub>35</sub> NO	I	73	111—112	1630	Methanol	33 <sup>b)</sup>
38	D	Methyl	Benzyl	C <sub>28</sub> H <sub>37</sub> NO	I	51	159—162	1610	Methanol	-21 <sup>a)</sup>
39	B	Ethyl	Benzyl	C <sub>29</sub> H <sub>43</sub> NO	I	83	106—108	1613	Isopropanol	-27
40	D	Ethyl	Benzyl	C <sub>29</sub> H <sub>39</sub> NO	I	63	124—125	1605	Methanol	19
41	A	Phenyl	Benzyl	C <sub>33</sub> H <sub>45</sub> NO	I	14	127—128	1625	Ethanol	-9
42	A	Benzyl	Benzyl	C <sub>34</sub> H <sub>47</sub> NO	I	67	53—59	1635	<i>n</i> -Hexane	-2
43	C	Benzyl	Benzyl	C <sub>34</sub> H <sub>43</sub> NO	II	73	(Oily)	1610	—	19

a) Significantly different from control,  $p < 0.05$ .

b) Significantly different from control,  $p < 0.01$ .

\*Dietary concentration of the test compound: 0.1%.

amides. It seems, therefore, that the concurrent presence of a secondary amide group and an aromatic ring as a constituent of the amine moiety is necessary for hypocholesterolemic action of these abietamide derivatives, and that as an acid moiety tetrahydroabietic or dihydroabietic acid is preferable in terms of activity to more unsaturated analogs such as abietic or dehydroabietic acid.

Thus, twenty benzylamide derivatives of  $\Delta^8$ -dihydroabietic acid were examined to investigate the effect of a substituent on the aromatic ring ( $R_1$ ) and/or the benzyl position ( $\alpha$ -position) ( $R_2$ ). As shown in Table II, the hypocholesterolemic activity was markedly enhanced by the introduction of a methoxy group at the 4-position of the aromatic ring in the amine moiety (49), whereas it was greatly reduced by the introduction of two methoxy groups at the 2- and 4-positions (53). In the case of monosubstitution at the aromatic ring, the activity was increased in the order of 4-methoxy (49), 2-chloro (50) and 2-methoxy (47). An increase in the activity was also obtained by substitution with a short alkyl straight chain or benzyl group at the  $\alpha$ -position of the amine moiety as represented by (25), (54), (55), (56), and (58). However, substitution with an *n*-decyl (56) or phenyl group (57) at the same position was far less effective. The enhancing effect of substitution at this position was thus in the decreas-

TABLE II. Hypocholesterolemic Activity of Benzylamide Derivatives of  $\Delta^8$ -Dihydroabietic Acid

No.	Structure		Formula	Yield (%)	mp (°C)	IR $\nu_{\max}$ (cm <sup>-1</sup> ); CON	Recrystn. solvent	Hypocholesterolemic activity			ID <sub>50</sub> ** (%)
	R <sub>1</sub>	R <sub>2</sub>						% inhibition			
								0.01 %*	0.03 %*	0.1 %*	
21	H	H	C <sub>27</sub> H <sub>39</sub> NO	83	125—126	1630	Methanol	4	25 <sup>a)</sup>	64 <sup>b)</sup>	0.07
44	2-Methyl	H	C <sub>28</sub> H <sub>41</sub> NO	63	121—122	1624	Methanol	14	31 <sup>a)</sup>	68 <sup>b)</sup>	0.06
45	3-Methyl	H	C <sub>28</sub> H <sub>41</sub> NO	59	108—110	1624	Acetone	2	32 <sup>b)</sup>	61 <sup>b)</sup>	0.06
46	4-Methyl	H	C <sub>28</sub> H <sub>41</sub> NO	74	130—132	1620	Methanol	24 <sup>a)</sup>	40 <sup>b)</sup>	60 <sup>b)</sup>	0.05
47	2-Methoxy	H	C <sub>28</sub> H <sub>41</sub> NO <sub>2</sub>	60	120—121	1625	Acetone	24 <sup>a)</sup>	47 <sup>b)</sup>	81 <sup>b)</sup>	0.03
48	3-Methoxy	H	C <sub>28</sub> H <sub>41</sub> NO <sub>2</sub>	71	114—115	1625	Methanol	13	25	60	0.07
49	4-Methoxy	H	C <sub>28</sub> H <sub>41</sub> NO <sub>2</sub>	68	129—130	1623	Methanol	62 <sup>b)</sup>	82 <sup>b)</sup>	93 <sup>b)</sup>	0.005
50	2-Chloro	H	C <sub>27</sub> H <sub>38</sub> ClNO	59	150—151	1624	Methanol	15	52 <sup>b)</sup>	69 <sup>b)</sup>	0.03
51	3-Chloro	H	C <sub>27</sub> H <sub>38</sub> ClNO	74	116—117	1622	Methanol	3	8	41 <sup>b)</sup>	0.15
52	4-Chloro	H	C <sub>27</sub> H <sub>38</sub> ClNO	64	161—164	1620	Methanol	14	24 <sup>b)</sup>	64 <sup>b)</sup>	0.06
53	2,4-Dimethoxy	H	C <sub>29</sub> H <sub>43</sub> NO <sub>3</sub>	56	(glassy)	1630	—	13	19	55 <sup>b)</sup>	0.08
25	H	Methyl	C <sub>28</sub> H <sub>41</sub> NO	91	125—128	1620	Methanol	41 <sup>b)</sup>	65 <sup>b)</sup>	93 <sup>b)</sup>	0.02
54	H	Ethyl	C <sub>29</sub> H <sub>43</sub> NO	90	102—109	1623	Isopropanol	43 <sup>b)</sup>	77 <sup>b)</sup>	86 <sup>b)</sup>	0.013
55	H	<i>n</i> -Amyl	C <sub>32</sub> H <sub>49</sub> NO	89	114—116	1630	<i>n</i> -Hexane	57 <sup>b)</sup>	73 <sup>b)</sup>	—	0.009
56	H	<i>n</i> -Decyl	C <sub>37</sub> H <sub>59</sub> NO	76	110—112	1630	<i>n</i> -Hexane	10	37 <sup>a)</sup>	—	0.05
57	H	Phenyl	C <sub>33</sub> H <sub>43</sub> NO	52	140—142	1625	Methanol	2	31 <sup>a)</sup>	69 <sup>b)</sup>	0.05
58	H	Benzyl	C <sub>34</sub> H <sub>45</sub> NO	68	167—170	1635	Ethylacetate	59 <sup>b)</sup>	78 <sup>b)</sup>	—	0.006
59	H	4-Methylbenzyl	C <sub>35</sub> H <sub>47</sub> NO	19	161—164	1650	Cyclohexane	32 <sup>b)</sup>	63 <sup>b)</sup>	—	0.019
60	4-Methoxy	Methyl	C <sub>29</sub> H <sub>43</sub> NO <sub>2</sub>	52	146—148	1630	Methanol	—7	45 <sup>b)</sup>	—	0.03
61	2-Hydroxy	Ethyl	C <sub>29</sub> H <sub>43</sub> NO <sub>2</sub>	58	211—214	1625	Acetone	16	47 <sup>b)</sup>	—	0.03

a) Significantly different from control,  $p < 0.05$ .

b) Significantly different from control,  $p < 0.01$ .

\* Dietary concentration of the test compound.

\*\* ID<sub>50</sub> represents the concentration of the test compound at which the serum cholesterol elevation is inhibited by 50%.

TABLE III. Effects of Compounds 13 and 19 on Serum and Liver Cholesterol

Test compound	No. of rats	Body weight (g)		Serum cholesterol		Liver weight (g)	Liver cholesterol		Acute toxicity LD <sub>50</sub> mg/kg, <i>i.p.</i>
		Initial	Gain	mg/dl	% inhibit.		mg/g liver	% inhibit.	
Normal	6	51 ± 2 <sup>a)</sup>	8 ± 0	124 ± 11	—	2.4 ± 0.1	4.7 ± 0.4	—	—
Control	24	49 ± 1	9 ± 1	415 ± 16	—	2.4 ± 0.1	18.7 ± 0.5	—	—
13*	6	49 ± 2	6 ± 1 <sup>b)</sup>	317 ± 23 <sup>c)</sup>	34	2.4 ± 0.1	7.3 ± 0.7 <sup>c)</sup>	81	>1600
19**	6	49 ± 2	3 ± 0 <sup>c)</sup>	117 ± 13	102	2.0 ± 0.1 <sup>c)</sup>	4.8 ± 0.3 <sup>c)</sup>	99	>1600

a) Mean ± S.E.

b) Significantly different from control,  $p < 0.05$ .

c) Significantly different from control,  $p < 0.01$ .

\*; A, H. cyclohexyl.

\*\*; B, H. phenyl.

The test compounds were added at a concentration of 0.1% to the cholesterol diet.

ing order of benzyl (58), *n*-amyl (55), ethyl (54), 4-methylbenzyl (59), methyl (25) and *n*-decyl (56). Substitution at both the aromatic ring and  $\alpha$ -position, as in 69 and 61, moderately enhanced the activity in comparison with the parent amide (21). As shown in Table III, compounds 13 and 19 did reduce not only the serum but also the liver cholesterol concentrations, the effect being more profound on the latter than on the former. These effects appear to be essentially the same as in the case of totarol, abietic acid and *N*-(2,6-dimethylphenyl)- $\Delta^8$ -dihydroabietamide.<sup>3)</sup> Therefore, the liver cholesterol-lowering action exerted by these abietamide derivatives may not be due to an altered distribution of cholesterol between the serum and liver. As suggested for abietic acid and totarol, these hypocholesterolemic effects may also be attributed to interference with the intestinal absorption of cholesterol (unpublished data).

### Chemistry

Abietic acid was purified by treating Chinese pine resin with boiling acetic acid by the method of Harris and Sanderson.<sup>4)</sup> The acid was precipitated as the diamylamine salt from acetone solution. After several recrystallizations of the salt from hot acetone, the free acid was regenerated by acidifying with acetic acid. Tetrahydroabietic acid was prepared as follows.<sup>5)</sup> A solution of abietic acid in acetic acid was hydrogenated with Adams' catalyst at room temperature under 100 atm. of H<sub>2</sub> for 6 hr. Dehydroabietic acid was prepared from commercial disproportionated pine resin in the manner described by Fieser and Campbell.<sup>6)</sup> Finely powdered pine resin was added to stirred and ice-cooled concentrated H<sub>2</sub>SO<sub>4</sub>. Stirring was continued for an additional hour, then the solution was added slowly to iced water with agitation. The precipitated material was collected by filtration. After extraction of the cake with boiling water, insoluble material was filtered off from the extract and the filtrate was acidified with concentrated HCl. On standing overnight at 5°, a colorless precipitate appeared. After recrystallization once from acetic acid, 12-sulfodehydroabietic acid was obtained as fine colorless needles. Hydrolysis of 12-sulfodehydroabietic acid was carried out using 60% H<sub>2</sub>SO<sub>4</sub> with stirring at 135° for 10 hr.  $\Delta^8$ -Dihydroabietic acid was prepared as follows.<sup>7)</sup> A mixture of a methanolic solution of Chinese pine resin and an aqueous solution of NaOH was hydrogenated with W-7 Raney nickel catalyst at 80 to 100° under 80 atm of H<sub>2</sub> for 6 hr. After removal of the catalyst by filtration, the filtrate was neutralized with methanolic hydrogen

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chloride. The mixture was then evaporated to dryness *in vacuo*. The solid residue was dissolved in ethanol and concentrated HCl was added. Refluxing the solution at 90° for 5 hr afforded  $\Delta^8$ -dihydroabietic acid. The solvent was removed *in vacuo* and the residue was dissolved in toluene. After washing with water the product was recovered by removal of the solvent. Four recrystallizations of the product from acetone gave  $\Delta^8$ -dihydroabietic acid.

In general, the amides were prepared according to methods I and II described in "Experimental".

### The Assay Method for Hypocholesterolemic Activity

As described previously,<sup>2)</sup> male Wistar rats aged 4 weeks were fed semisynthetic basal and cholesterol-containing diets *ad libitum* for 3 days, then killed following an overnight fast to determine the serum and liver cholesterol. The test compounds were added to the cholesterol diet. The hypocholesterolemic activity was expressed as the % inhibition of serum cholesterol elevation induced by cholesterol feeding or as ID<sub>50</sub>.

For acute toxicity tests, the compounds were suspended at a concentration of 1% to 0.5% CMC and were administered intraperitoneally to ddY male mice weighing 25–32 g.

### Experimental

The melting points were determined in open capillaries with a Büchi melting point apparatus and are uncorrected. The boiling points of oily compounds were not determined. IR spectra were measured with a Hitachi 215 spectrometer. NMR spectra were measured with a Varian A-60 spectrometer with TMS as an internal standard.

#### Method I

**N-Phenyl- $\Delta^8$ -dihydroabietamide (19)**—A mixture of 4.80 g (15.8 mmol) of  $\Delta^8$ -dihydroabietic acid and 5.60 g (47.3 mmol) of SOCl<sub>2</sub> in 30 ml of benzene was refluxed for 2 hr. A pale brown oily product was obtained by removal of the solvent and excess SOCl<sub>2</sub> under reduced pressure. This crude acid chloride (IR: 1783 cm<sup>-1</sup>) was used without purification. The acid chloride, dissolved in 30 ml of benzene, was added dropwise with agitation at room temperature to a mixture of 1.59 g (15.8 mmol) of Et<sub>3</sub>N and 1.47 g (15.8 mmol) of aniline dissolved in 20 ml of benzene. After additional agitation for 3 hr, the reaction mixture was washed with 5% HCl, H<sub>2</sub>O, 5% NaOH and H<sub>2</sub>O in that order. The organic layer was dried over anhydr. MgSO<sub>4</sub> and filtered. Benzene was removed and the residual mass was crystallized out from a small amount of isopropanol. Recrystallization from EtOH gave 5.19 g (92%) of colorless needles melting at 151–152°: IR: 1640 cm<sup>-1</sup> (CONH). *Anal.* Calcd for C<sub>26</sub>H<sub>37</sub>NO: C, 82.27; H, 9.83; N, 3.69. Found: C, 82.70; H, 9.81; N, 3.85. NMR (CCl<sub>4</sub>)  $\delta$ : 0.90 (6H, d,  $J=6$  Hz, two methyls of isopropyl), 0.95 (3H, s, C10-CH<sub>3</sub>), 1.21 (3H, s, C4-CH<sub>3</sub>), 6.79–7.50 (5H, m, phenyl).

**N-Benzyltetrahydroabietamide (20)**—An acid chloride prepared from 3.06 g (10 mmol) of tetrahydroabietic acid and an excess of SOCl<sub>2</sub> was added to 10 ml of pyridine, and 3.22 g (30 mmol) of benzylamine was added to the mixture with agitation and ice-cooling for 30 min. The pyridine was removed under reduced pressure and 100 ml of ether was added to the residue. The insoluble matter was removed by filtration, and the filtrate was worked up by the procedure described above. The ether layer was dried over anhydr. MgSO<sub>4</sub> and filtered. The ether was removed and the residue was crystallized from hexane to give 3.01 g (76%) of colorless needles melting at 112–114°: IR: 1640 cm<sup>-1</sup> (CONH). *Anal.* Calcd for C<sub>23</sub>H<sub>30</sub>NO: C, 79.94; H, 11.83; N, 4.05. Found: C, 80.09; H, 11.4; N, 4.34. NMR (CDCl<sub>3</sub>)  $\delta$ : 0.85 (6H, d,  $J=6$  Hz, two methyls of isopropyl), 0.90 (3H, s, C10-CH<sub>3</sub>), 1.20 (3H, s, C4-CH<sub>3</sub>), 4.50 (2H, d,  $J=5$  Hz, CH<sub>2</sub>), 7.32 (5H, s, phenyl).

**N-Methyl-N-phenyldehydroabietamide (37)**—An acid chloride prepared from 2.20 g (7.3 mmol) of dehydroabietic acid and an excess of SOCl<sub>2</sub> (2.61 g, 22 mmol) was dissolved in 10 ml of acetone. The acid chloride solution was added dropwise to a stirred solution of 2.00 g (18.7 mmol) of N-methylaniline in 10 ml of acetone with stirring. After agitation for 3 hr, the reaction mixture was poured into 100 ml of water. The precipitated crystalline mass was collected by decantation. Crystallization from MeOH gave 2.10 g (73%) of colorless needles melting at 111–112°: IR: 1630 cm<sup>-1</sup>. *Anal.* Calcd for C<sub>27</sub>H<sub>35</sub>NO: C, 83.24; H, 9.06; N, 3.60. Found: C, 82.89; H, 9.38; N, 3.79. NMR (CDCl<sub>3</sub>)  $\delta$ : 0.85 (3H, s, C10-CH<sub>3</sub>), 1.11 (3H, s, C4-CH<sub>3</sub>), 1.20 (6H, d,  $J=7$  Hz, two methyls of isopropyl), 3.20 (3H, s, N-CH<sub>3</sub>), 6.87–7.02 (3H, aromatic protons of ring C), 7.16–7.40 (5H, m, phenyl).

#### Method II

**N-Methyl-N-cyclohexylabietamide (33)**—A liquid mixture comprising 5.86 g (10 mmol) of abietic anhydride, 2.26 g (20 mmol) of N-methylcyclohexylamine and 50 ml of xylene was heated under reflux for 8 hr. The reaction mixture was cooled and washed with 3% KOH aq. solution, H<sub>2</sub>O, 3% HCl and H<sub>2</sub>O in that order. The xylene layer was dried over anhydr. MgSO<sub>4</sub> and filtered. The xylene was removed under reduced pressure, and the residual oil crystallized on standing. Recrystallization from acetone gave 3.15 g

(79%) of colorless scales melting at 130–132°: IR: 1610  $\text{cm}^{-1}$  (CON). *Anal.* Calcd for  $\text{C}_{27}\text{H}_{42}\text{NO}$ : C, 81.55; H, 10.90; N, 3.52. Found: C, 81.53; H, 11.10; N, 3.71; NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.83 (6H, d,  $J=5$  Hz, two methyls of isopropyl), 1.06 (3H, s, C10- $\text{CH}_3$ ), 1.34 (3H, s, C4- $\text{CH}_3$ ), 2.83 (3H, s, N- $\text{CH}_3$ ), 5.38 (1H, C7-CH), 5.78 (1H, C14-CH).

**N,N-Dimethylabietamide (31)**—A mixture of 2.93 g (5 mmol) of abietic anhydride, 5 ml (20 mmol) of 20% aq. solution of dimethylamine and 20 ml of EtOH was refluxed for 2 hr. After removal of EtOH *in vacuo*, the residue was dissolved in 20 ml of benzene and washed with 5% NaOH aq. solution and  $\text{H}_2\text{O}$  in that order. The benzene was removed and a brown glassy residue was obtained (73%). Purification of 0.3 g of the residue was carried out by preparative TLC, using  $\text{CHCl}_3$  as an eluent. An almost colorless glassy product was obtained: IR: 1600  $\text{cm}^{-1}$  (CON). *Anal.* Calcd for  $\text{C}_{29}\text{H}_{35}\text{NO}$ : C, 80.19; H, 10.71; N, 4.25. Found: C, 79.89; H, 11.23; N, 4.32. NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.95 (6H, d,  $J=6$  Hz, two methyls of isopropyl), 1.09 (3H, s, C10- $\text{CH}_3$ ), 1.35 (3H, s, C4- $\text{CH}_3$ ), 3.05 (6H, s, two N- $\text{CH}_3$ ), 5.35 (1H, C7-CH), 5.76 (1H, C14-CH).

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