Retinobenzoic Acids. 4. Conformation of Aromatic Amides with Retinoidal Activity. Importance of *trans*-Amide Structure for the Activity

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N-Methylation of two retinoidal amide compounds, 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carbamoyl]benzoic acid (**3**, Am80) and 4-[[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carbonyl]amino]benzoic acid (**5**, Am580), resulted in the disappearance of their potent differentiation-inducing activity on human promyelocytic leukemia cell line HL-60. Studies with ^{1}H NMR and UV spectroscopy indicated that large conformational differences exist between the active *secondary* amides and the inactive *N*-methyl amides. From a comparison of the spectroscopic results of these amides with those of stilbene derivatives, the conformations of the active amides are expected to resemble that of (*E*)-stilbene, whereas the inactive amides resemble the *Z* isomer: **3** (Am80) and **5** (Am580) have a *trans*-amide bond and their whole structures are elongated, while the N-methylated compounds [**4** (Am90) and **6** (Am590)] have a *cis*-amide bond, resulting in the folding of the two benzene rings. These structures in the crystals were related to those in solution by ^{13}C NMR spectroscopic comparison between the two phases (solid and solution).

Retinobenzoic acids are defined as "a series of benzoic acid derivatives with potent retinoidal activities (that is, the specific activities of retinoic acid)".[1,2] They modulate the cellular differentiation and proliferation in many types of cells in the cases where retinoic acid (**1**) acts as a modulator.[3,4] Their mechanism of action seems to be the same as that of retinoic acid,[5,6] and since they probably also bind to the same receptor,[7] they are biologically classified as "retinoids" (Chart I).[3,8] In the generic chemical structure of retinobenzoic acids, represented by **2**, R is a medium-sized alkyl group(s), such as isopropyl or *tert*-butyl. In particular, a *m*-alkyl group is necessary for the activity. Another group required is the carboxyl group at the para position of the other benzene ring. The linking group X can be varied, such as —NHCO—,[9] —CONH—,[10] —SO_2NH—, —COC=C—,[11] —N=N—[12] and so on. Among synthesized retinobenzoic acids, two types of benzanilides, 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carbamoyl]benzoic acid acid (**3**, Am80) and 4-[[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carbonyl]amino]benzoic acid (**5**, Am580), showed very strong retinoidal activities in several assay systems.[1] For example, **3** (Am80) and **5** (Am580) are several times more active than retinoic acid in terms of differentiation-inducing activity on human promyelocytic leukemia cell line HL-60 (Table I). However, in the course of studies of the structure–activity relationships of these retinoidal amides, it was found that the introduction of a methyl group on the N atom of the amide moiety of **3** (Am80) or **5** (Am580) [yielding **4** (Am90) or **6** (Am590), respectively] resulted in the 10^4-fold reduction of the activity (Table I), though the methyl group can be suprafacially supposed to correspond to the methyl group on the

Chart I

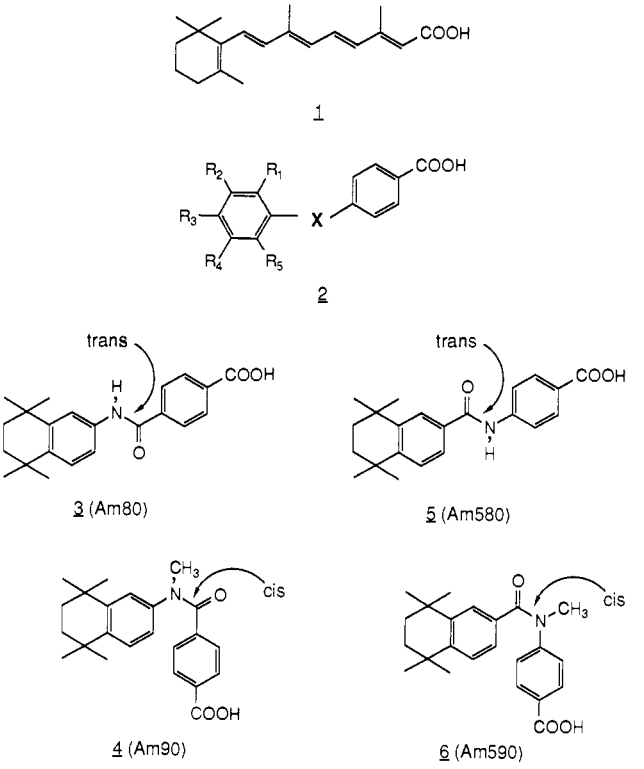

Table I. Differentiation-Inducing Activities of Retinoidal Amide Compounds on HL-60 Cells

compd	ED_{50}, M	rel. act.[c]
retinoic acid	2.4×10^{-9}	100
3 (Am80)[a]	7.9×10^{-10}	350
4 (Am90)[a]	$>10^{-6}$ [d]	$<10^{-2}$
12 (Am93)[b]	6.5×10^{-8}	2.6
13 (Am95)[b]	1.5×10^{-7}	1.1
5 (Am580)[a]	3.4×10^{-10}	720
6 (Am590)[a]	$>10^{-6}$	$<10^{-2}$
14 (Am595)[b]	5.1×10^{-7}	0.33

[a] For structures, see Chart I. [b] For structures, see Figure 2. [c] Relative activity is defined as the mean value of the ratio of ED_{50} (retinoic acid) to ED_{50} (test compound), both values having been obtained in concurrent experiments. [d] $>10^{-6}$ M means slightly active at 10^{-6} M.

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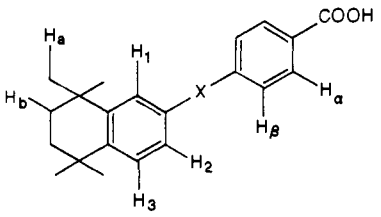
Table II. ^{1}H NMR Chemical Shifts of Amide and Stilbene Derivatives[a]



	H_a	H_b	H_1	H_2	H_3	H_α	H_β	others
3 (Am80)	1.27, 1.30	1.71	7.65	7.45	7.31	8.13	7.99	
4 (Am90)	0.96, 1.20	1.59	6.82	7.02	7.28	7.81	7.31	3.46 (NCH_3)
5 (Am580)	1.31, 1.34	1.74	7.93	7.69	7.47	8.01	7.84	
6 (Am590)	0.94, 1.20	1.59	7.05	7.22	7.27	7.90	7.20	3.50 (NCH_3)
7 (St80)[b]	1.28, 1.32	1.71	7.48	7.38	7.32	7.98	7.63	7.15, 7.27
8 (St88)[b]	1.04, 1.24	1.64	7.13	6.96	7.20	7.87	7.33	6.59, 6.65

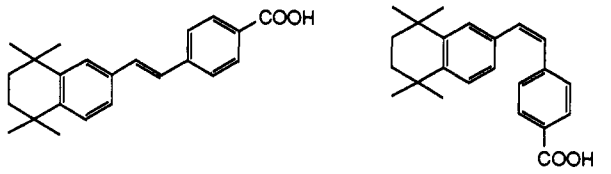
[a] Chemical shifts are expressed in ppm relative to Me_4Si in CD_3OD. [b] For structures, see Chart II.

polyene chain of retinoic acid. Considering the fact that the amide moiety can be inverted without any reduction of the activity [3 (Am80) vs 5 (Am580)] and the variety of permissible linking groups X in generic formula 2, it does not seem plausible that the remarkable disappearance of the activity of the *N*-methyl compounds is attributable to the direct change of electronic properties caused by N-methylation or to the presence of the hydrogen on the N atom of the amide group as the proton donor in hydrogen bonding with the receptor. The third possibility is that stereochemical changes caused the *N*-methyl amides to be inactive. Spectroscopic studies indeed showed dramatic conformational differences between the active and the inactive amides. In this paper, we report the results of detailed conformational studies of these retinoidal amides.

Results

Comparison of the ^{1}H NMR spectra of retinoidal amide compounds showed large differences in chemical shifts between 3 (Am80) and 4 (Am90) or between 5 (Am580) and 6 (Am590) (Table II). As a whole, the absorptions of the *tertiary* amides are shifted to higher fields. In the aromatic region, the absorption of protons ortho to the amide group (H_1, H_2, and H_β) of 3 (Am80) are shifted to lower field, at least partially due to the anisotropy of the amide carbonyl group. However, the signals of these protons of 4 (Am90) appear at 0.4–0.8 ppm higher fields than those of 3 (Am80). This tendency is also seen with the other aromatic protons (H_3 and H_α), though to a lesser degree. Similarly, 6 (Am590) has these aromatic protons more shielded than 5 (Am580), to the same degree as the difference between 3 (Am80) and 4 (Am90). Thus, the interaction of two benzene rings of the *N*-methyl amide compounds is very different from that of the *secondary* amide compounds. More significantly, similar shifts to higher field are shown by the aliphatic protons (the methyl groups on the ring and the ring methylene groups), though these protons should be little affected by the electronic properties of the amide group. One of the two singlet signals of the four methyl groups on the ring is shifted to 0.2 ppm higher field in 4 (Am90) and 6 (Am590) than in 3 (Am80) or 5 (Am580). Signals corresponding to methylene protons are also shifted to 0.1–0.2 ppm higher field in 4 (Am90) and 6 (Am590). These results indicated the conformational change of the amide bonds, with a consequent change of the whole molecular structures and the spatial relationship of the two benzene rings. This change became much clearer when comparing the chemical shift difference between (*E*)- and (*Z*)-stilbene derivatives 7 (St80) and 8 (St88), respectively (Chart II), where the

Chart II



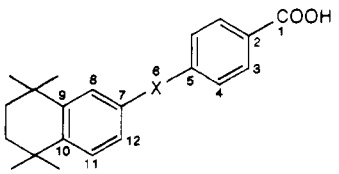
7 (St80) 8 (St88)

linking group between the two benzene rings is an ethylenic bond instead of the amide bond. In this case, the *Z* isomer has the proton signals shifted to higher field in both aromatic and aliphatic regions. Interestingly, the chemical shift values and differences of aliphatic methyl and methylene protons of the two isomers agreed well with those of the amide compounds. Therefore, the conformational structures of 3 (Am80) and 5 (Am580) should be similar to that of (*E*)-stilbene 7 (St80), and the structures of 4 (Am90) and 6 (Am590) should be similar to that of the *Z* isomer 8 (St88).

The ^{13}C NMR spectra could be classified into two types according to this stereochemical difference of the amide bonds (Table III). All signals, including those of quaternary carbons, were assigned by CH-COSY (and long-range CH-COSY). In this case, the amide carbonyl carbons (C_6) and the carbons ipso or ortho to the amide N atoms [$C_{7,8,12}$ in 4 (Am90) and $C_{4,5}$ in 6 (Am590)] are shifted to 4–7 ppm lower fields. These shifts may result from the different electronic effects of the amide group due to its conformational change.

This assumption of conformational differences is also supported by the UV spectra of the four amides and of the two stilbene derivatives (Table IV). Both isomers of stilbenes have three absorption maxima in the region of 200–400 nm. The most remarkable difference between the spectra of the two isomers is that in the *Z* isomer the absorption corresponding to that at 329 nm ($\log \epsilon = 4.54$) of the *E* isomer is shifted to a shorter wavelength (316 nm) and its absorbance is diminished ($\log \epsilon = 4.08$). This tendency can be seen in the amide compounds. Comparing the absorption maxima at the longest wavelength [286 nm, $\log \epsilon = 4.19$ for 3 (Am80) and 283 nm, $\log \epsilon = 4.44$ for 5 (Am580)], those of the *tertiary* amides are shifted to shorter wavelengths and their absorbances are reduced by half [274 nm, $\log \epsilon = 3.84$ for 4 (Am90) and 260 nm, $\log \epsilon = 4.13$ for 6 (Am590)]. Thus, the conformational relationship between 3 (Am80) and 4 (Am90) or between 5 (Am580) and 6 (Am590) is quite similar to that of the *E* and *Z* isomers of stilbene derivatives. That is, the conformations of the amide bonds of 3 (Am80) and 5 (Am580)

Table III. ^{13}C NMR Chemical Shifts of Retinoidal Amide Compounds[a]



	3 (Am80)	4 (Am90)	5 (Am580)	6 (Am590)
C_1	168.7	168.7	167.0	166.6
C_2	134.5	132.5	125.4	128.1
C_3	130.7	130.0	130.2	130.0
C_4	128.5	129.3	119.6	126.6
C_5	140.3	141.8	143.4	148.9
C_6	167.7	171.8	166.0	169.3
C_7	136.9	142.4	131.9	132.3
C_8	120.2	127.1	125.8	127.1
C_9	146.4	146.9	144.6	143.3
C_{10}	142.5	144.9	148.5	146.3
C_{11}	127.8	128.7	126.5	126.2
C_{12}	120.0	124.3	124.9	126.0
NCH_3	-	38.1	-	37.6
others	36.1 (t)	35.8 (t)	34.5 (t)	34.3 (t)
		35.7 (t)	34.3 (t)	34.2 (t)
	35.2 (s)	35.0 (s)	34.2 (s)	33.9 (s)
	34.8 (s)	34.8 (s)	34.1 (s)	33.6 (s)
	32.2 (q)	32.0 (q)	31.5 (q)	31.3 (q)
		31.7 (q)	31.4 (q)	31.0 (q)

[a] Chemical shifts are expressed in ppm relative to Me_4Si in CD_3OD [for 3 (Am80) and 4 (Am90)] or DMSO-d_6 [for 5 (Am580) and 6 (Am590)].

Table IV. UV Spectral Data for Amide and Stilbene Derivatives[a]

compd	λmax (log ε)
3 (Am80)	286 (4.19), 236 (4.43), 208 (4.47)
4 (Am90)	274 (sh) (3.84), 227 (4.30), 210 (4.36)
5 (Am580)	283 (4.44), 240 (sh) (4.08), 208 (4.60)
6 (Am590)	260 (sh) (4.13), 239 (sh) (4.21), 208 (4.58)
7 (St80)	329 (4.54), 237 (4.04), 207 (4.24)
8 (St88)	316 (4.08), 239 (4.20), 207 (4.25)

[a] Wavelengths of maximum absorbance are given in nm and the molar absorption coefficients are expressed in logarithmic values.

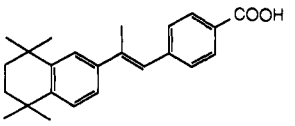
are nearly that of a trans ethylenic bond and, on the contrary, those of 4 (Am90) and 6 (Am590) are nearly that of a cis ethylenic bond.

The crystal structures[13] revealed conformational changes, which correspond well to the structures expected from the spectroscopic data in solution: the amide bonds of 3 (Am80) and 5 (Am580) are trans, while those of 4 (Am90) and 6 (Am590) are cis. Furthermore, each pair of ^{13}C NMR spectra (solid and solution states) of the four compounds, shown in Figure 1, had a similar tendency in their chemical shifts as a whole. That is, the structures deduced from X-ray analyses appear to be maintained in solution.

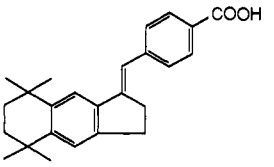
Discussion

The amide bond has an interesting role in many biologically active compounds. In these retinoidal amides, surprisingly, the simple process of N-methylation caused a dramatic diminution of the activities. NMR and UV spectroscopies revealed conformational differences owing to amide trans and cis isomerism, and this was supported by a comparison of the spectra of (*E*)- and (*Z*)-stilbene derivatives with those of the amide compounds. The higher field shifts in the ^1H NMR spectra of the cis compounds [4, (Am90), 6 (Am590), and 8 (St88)] resulted from the change of the anisotropic effects of (1) the amide carbonyl group, especially on the protons of the benzene rings, and (2) the two overlapping benzene rings, which interact with each other. The aliphatic protons are also affected (more strongly shielded) by the other benzene ring. These results and the similarity of ^{13}C NMR spectra in the solid state and in solution for each compound indicate that the structures in the crystalline state are largely maintained in solution. The ^1H NMR chemical shifts do not change with temperature (−30 to 100 °C) and are little affected by the nature of the solvent ($CDCl_3$, CD_3OD, etc.). This means that there exists only one conformer of the amide structure in solution for each compound, and cis–trans interconversion does not occur in this temperature range.

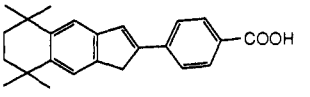
Chart III



9 (TTNPB)



10 (Ex80)



11 (In80)

N-Methylation caused a large conformational change in retinoidal benzanilides. The simple (unsubstituted) benzanilide has a *trans*-amide bond both in solution and in the crystal.[14,15] On the other hand, *N*-methylbenzanilide has been little studied and even its structure in the crystal is unknown, though its conformation in solution is considered to be very different from that of benzanilide.[16] The preference of the cis form seems to be a general character of *N*-methylbenzanilides. We are currently investigating on the generality of *cis*-amide (especially tertiary amide) conformations.

There is another conformational feature of retinoidal-active amides 3 (Am80) and 5 (Am580) that may be significant: the stereochemistry of the Ar–amide single bond (Figure 2). This single bond may rotate energetically more readily than the amide bond itself. It is of interest to know which is the form that is responsible for the retinoidal actions. Previously we studied the activities of conformationally restricted analogues of the retinoidal stilbene 9 (TTNPB)[17] (Chart III). In this case, 10 (Ex80), restricted to the "s-cis" form, is more active than 9 (TTNPB) or 11 (In80), which is fixed in "s-trans" form. Similarly, compounds in which the amide bond is fixed by a ring were designed (Figure 2). The acylindole 12 (Am93) and the acylindoline 13 (Am95) derivatives correspond to the "s-cis" form of 3 (Am80), and also to 10 (Ex80) or to the "s-cis" form of 9 (TTNPB). The oxoisoindole derivative 14 (Am595) corresponds to the "s-cis" form of 5 (Am580) or the "s-trans" form of 9 (TTNPB) [11 (In80)]. This

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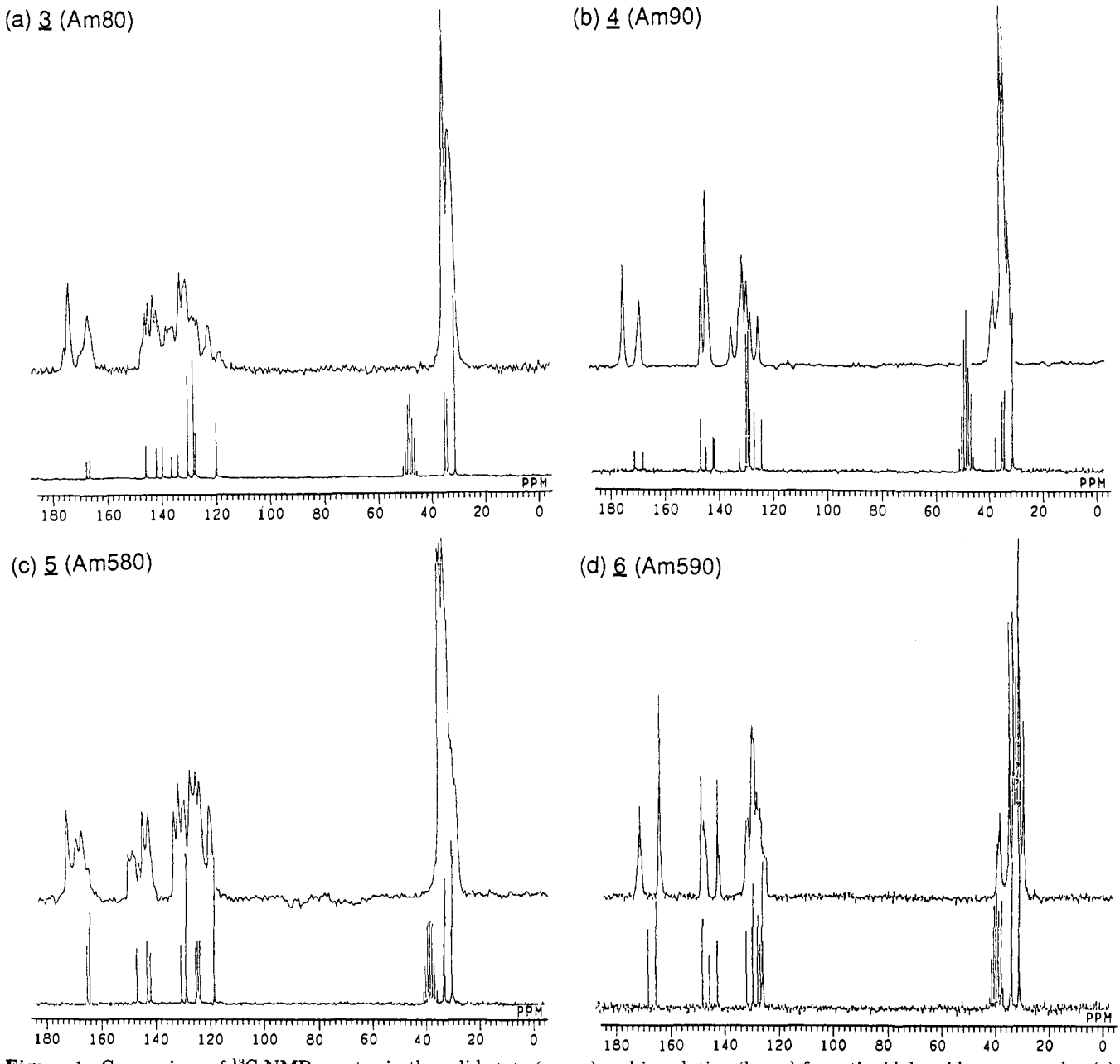

Figure 1. Comparison of ^{13}C NMR spectra in the solid state (upper) and in solution (lower) for retinoidal amide compounds: (a) **3** (Am80), (b) **4** (Am90), (c) **5** (Am580), and (d) **6** (Am590). The solvent was CD_3OD for a and b and DMSO-d_6 for c and d.

compound can be regarded as restricted to the "s-trans" form of **3** (Am80), since the amide bond can be reversed without change of activity [**3** (Am80) vs **5** (Am580)]. The activities of these conformationally restricted amide compounds are shown in Table I. Though their activities are weaker than that of **3** (Am80) or **5** (Am580), **12** (Am93) has the strongest activity of the three compounds, and **13** (Am95) is significantly more active than **14** (Am595). The structure–activity relation is not entirely clear. However, the reduction of activity (less than $^1/_{1000}$) of **14** (Am595) from **5** (Am580) is greater than that ($^1/_{100}$) of **13** (Am95) from the corresponding amide, **3** (Am80). This result may suggest that the s-cis form of **3** (Am80) and the s-trans form of **5** (Am580) seem to be the preferred conformers. There are several possible explanations for the weaker activities of **12** (Am93) and **13** (Am95). In **12** (Am93), the acyl–indole amide bond can be more easily hydrolyzed than the amide bond of **3** (Am80), **5** (Am580), or **14** (Am595). A ^1H NMR study showed that **13** (Am95) exists in equilibrium between *trans*- and *cis*-amide conformers in solution. Thus, the amide bond might not be fixed in **12** (Am93) and **13** (Am95) as expected, and other factors would also affect the activity.

The torsion angles between N and Ph or CO and Ph do definitely affect the conformational orientation of the moieties required for the activity. It is likely that subtle differences of this torsion angle greatly affect the mutual orientation of two important structural moieties, the hydrophobic alkyl group on the left benzene ring and the carboxyl group. Many types of retinoidal compounds, beside the amide compounds considered here, are now available, and detailed conformational studies are required to elucidate the essential molecular structure for the retinoidal actions.

Experimental Section

The human promyelocytic leukemia cells HL-60 were provided by Prof. F. Takaku (Faculty of Medicine, University of Tokyo). The cell culture and the method for the assay of differentiation of HL-60 cells were described in the previous paper.[1] ED_{50} values of active compounds were calculated from the Nitroblue tetrazolium (NBT) reduction assay data. Relative activities were calculated as the ratio of ED_{50} of retinoic acid to ED_{50} of the test

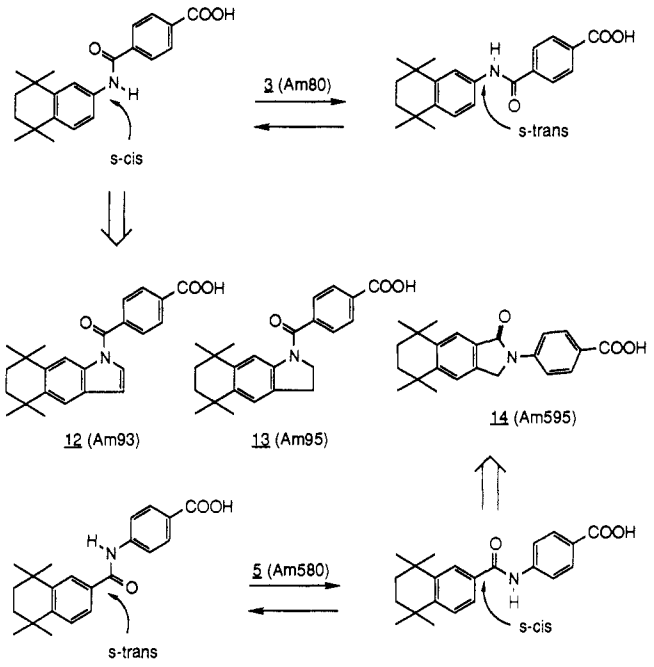

Figure 2. Conformational restriction of retinoidal-active amides.

compound obtained in concurrent experiments.

The retinoidal amide compounds [**3**, (Am80), 4 (Am90), **5** (Am580), and **6** (Am590)] were prepared by the method reported previously.[1] ^{1}H NMR spectra were obtained on a JEOL GX 400-MHz NMR or a JEOL FX 100-MHz NMR spectrometer. Proton chemical shifts are expressed in ppm relative to tetramethylsilane (TMS). ^{13}C NMR spectra were recorded on a JEOL GX 400 (at 100 MHz) and chemical shifts are given in ppm relative to TMS. The spectra were referenced to the resonance of the solvent (CD_3OD, 49.0 ppm; $(CD_3)_2SO$, 39.5 ppm). UV spectra were measured in 95% EtOH, on a Shimadzu UV200S. The solid-state ^{13}C NMR were taken with a JEOL GX 270-MHz NMR spectrometer, by the technique of cross-polarization and magic-angle sample spinning, referenced to external adamantane (29.50 ppm).

4-[(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-1*H*-benz[*f*]indol-1-yl)carbonyl]benzoic Acid (12, Am93). Tris(dimethylamino)methane (3.6 mL, 20.8 mmol) was added to a solution of 1,2,3,4-tetrahydro-1,1,4,4,6-pentamethyl-7-nitronaphthalene (2.85 g, 11.5 mmol) in 30 mL of DMF under Ar gas, and the mixture was heated at 115 °C for 24 h. The mixture was cooled to room temperature, and then semicarbazide hydrochloride (8.5 g, 76.2 mmol) in 15 mL of H_2O was added to the solution. After 20 min, the precipitates were collected and dissolved in CH_2Cl_2. The organic layer was washed with H_2O and dried over $MgSO_4$. After evaporation, the crude product was recrystallized from CH_3OH to give 2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-nitronaphthalen-2-yl)ethanal semicarbazone (99%). The semicarbazone (1.5 g, 4.86 mmol) was dissolved in CH_3OH and hydrogenated on 10% Pd–C (1.0 g) to give 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-1*H*-benz[*f*]indole (quant. yield). Next, 65 mg of NaH (60% purity, 1.63 mmol) was washed twice with *n*-hexane and suspended in 30 mL of dry DMF. The indole (327 mg, 1.44 mmol) was added and the mixture was stirred for 1 h. Terephthalic acid monobenzyl ester chloride was added to this solution at 0 °C and the mixture was stirred for 3 h. The solvent was removed under vacuum and the residue was diluted with AcOEt and H_2O. The organic layer was washed with water and brine and dried over $MgSO_4$. After evaporation, the residue was chromatographed on silica gel to give benzyl 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-1*H*-benz[*f*]indol-1-yl)carbonyl]benzoate (43.9%). This benzyl ester (97 mg, 0.208 mmol) was hydrogenated on 10% Pd–C (40 mg) in 40 mL of EtOH for 45 min to give **12** (Am93) (quant. yield) **12** (Am93): colorless prisms (from EtOH) mp 273 °C dec; ^{1}H NMR (100 MHz, $CDCl_3$) 1.37 (s, 12 H), 1.78 (s, 4 H), 6.81 (d, 1 H, J = 4 Hz), 7.26 (d, 1 H, J = 4 Hz), 7.60 (s, 1 H), 7.90 (d, 2 H, J = 8 Hz), 8.22 (d, 2 H, J = 8 Hz), 8.31 (s, 1 H). Anal. ($C_{24}H_{25}NO_3$) C, H, N.

4-[(2,3,5,6,7,8-Hexahydro-5,5,8,8-tetramethyl-1*H*-benz[*f*]indol-1-yl)carbonyl]benzoic Acid (13, Am95). To a solution of the 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-1*H*-benz[*f*]indole [300 mg, 2.56 mmol; see the section on **12** (Am93)] in 7 mL of AcOH, was added $NaB(CN)H_3$ (494 mg, 7.86 mmol) under Ar gas, and the mixture was stirred at 15 °C for 2 h. The mixture was poured into water, basified by adding 1 N $NaHCO_3$, and then extracted with ether. The organic layer was washed with water and dried over $MgSO_4$. The crude 2,3,5,6,7,8-hexahydro-5,5,8,8-tetramethyl-1*H*-benz[*f*]indole was obtained by the removal of the solvent (quant. yield). This amine (148 mg, 0.65 mmol) was dissolved in 7 mL of pyridine. Terephthalic acid monomethyl ester chloride (155 mg, 0.78 mmol) and a catalytic amount of 4-(dimethylamino)pyridine was added, and the mixture was stirred for 30 min. The mixture was poured into water and extracted with AcOEt. The organic layer was washed with aqueous $Cu(NO_3)_2$, water, and brine and dried over $MgSO_4$. After evaporation, the crude product was chromatographed on silica gel to give methyl 4-[(2,3,5,6,7,8-hexahydro-5,5,8,8-tetramethyl-1*H*-benz[*f*]indol-1-yl)carbonyl]benzoate (71%), which was hydrolyzed by the usual method (aqueous KOH/CH_3OH) to give **13** (Am95) (94%). **13** (Am95): colorless prisms (from CH_3OH), mp 264.5–266 °C; ^{1}H NMR (100 MHz, acetone-d_6) 1.25 (s, 12 H), 1.68 (s, 4 H), 3.05 (t, 2 H, J = 8 Hz), 4.00 (t, 2 H, J = 8 Hz), 7.20 (s, 1 H), 7.65 (d, 2 H, J = 9 Hz), 8.14 (d, 2 H, J = 9 Hz); IR (KBr) 1640, 1690 cm^{-1}. Anal. ($C_{24}H_{27}NO_3$) C, H, N.

4-(2,3,5,6,7,8-Hexahydro-5,5,8,8-tetramethyl-1-oxo-1*H*-benz[*f*]isoindol-2-yl)benzoic Acid (14, Am595). A mixture of methyl 5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthoate (1.2 g, 4.62 mmol), *N*-bromosuccinimide (1.0 g, 5.62 mmol), and azobisisobutyronitrile (200 mg) was dissolved in 60 mL of CCl_4. The mixture was refluxed for 4 h and then cooled to 0 °C and diluted with 10 mL of *n*-hexane. After filtration and evaporation, the residual yellow oil was chromatographed on silica gel to give methyl 3-(bromomethyl)-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthoate (91.9%). The bromide (160 mg, 0.45 mmol) and ethyl *p*-aminobenzoate (300 mg) were dissolved in 10 mL of CH_3OH and stirred for 2 days. After evaporation, the residue was extracted with ether. The organic layer was washed with 1 N HCl (several times), water, and brine, dried over $MgSO_4$, and chromatographed on silica gel to give ethyl 4-(2,3,5,6,7,8-hexahydro-5,5,8,8-tetramethyl-1-oxo-1*H*-benz[*f*]isoindol-2-yl)benzoate (79.5%), which was hydrolyzed by a usual method to give **14** (Am595) (88.2%). **14** (Am595): colorless prisms (from AcOEt–*n*-hexane) mp >300 °C; ^{1}H NMR (100 MHz, DMSO-d_6) 1.33 (s, 12 H), 1.71 (s, 4 H), 4.98 (s, 2 H), 7.63 (s, 1 H), 7.72 (s, 1 H), 8.01 (s, 4 H). Anal. ($C_{23}H_{25}NO_3$) C, H, N.

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Registry No. **3**, 94497-51-5; **4**, 110383-33-0; **5**, 102121-60-8; **6**, 116193-58-9; **7**, 119454-82-9; **8**, 121866-06-6; **12**, 121866-07-7; **12** benzyl ester, 121866-12-4; **13**, 121866-08-8; **13** methyl ester, 121866-14-6; 14, 121866-09-9; 14 methyl ester, 121866-17-9; $C_6H_5CH_2OCOC_6H_4$-4-COCl, 67852-95-3; $CH_3OCOC_6H_4$-4-COCl, 7377-26-6; $C_2H_5OCOC_6H_4$-4-NH_2, 94-09-7; 1,2,3,4-tetrahydro-1,1,4,4,6-pentamethyl-7-nitronaphthalene, 116233-16-0; 2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-nitronaphthalen-2-yl)-ethanal semicarbazone, 121866-10-2; 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-1*H*-benz[*f*]indole, 121866-11-3; 2,3,5,6,7,8-hexahydro-5,5,8,8-tetramethyl-1*H*-benz[*f*]indole, 121866-13-5; methyl 5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthoate, 121866-15-7; methyl 3-(bromomethyl)-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthoate, 121866-16-8.