# Spectroscopic Characterization of 13-*cis*- and *all-trans*-Retinamides

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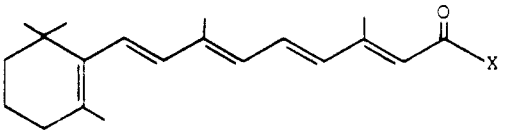
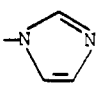
**Data from determinations of the $^1H$ and $^{13}C$ NMR, UV, IR, and mass spectra of some 13-*cis*- and *all-trans*-retinamides are reported. Characteristic shifts in the $^{13}C$ and $^1H$ NMR spectra of the 13-*cis*-retinamides readily distinguish them from the corresponding all-trans isomers. The mass spectra include strong molecular-ion and characteristic fragment peaks. The main UV maximum of the 13-cis amides shows a slight shift to longer wavelength (2–4 nm) from that of the all-trans amides and a lower molar absorptivity. Selected infrared bands are listed.**

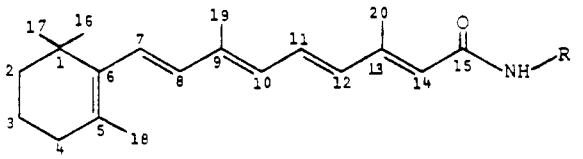
## Introduction

The purpose of this report is to describe the characterization of several *all-trans*-retinamides (II) and 13-*cis*-retinamides (IV)



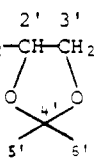
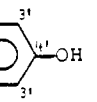
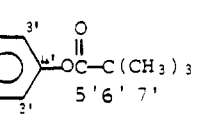
I

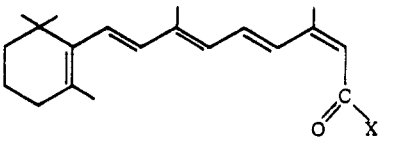
a, X = OH; b, X = Cl; c, X = 



II

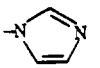
| | R |
|---|---|
| a, | $-CH_3$ 1' |
| b, | $-CH_2CH_3$ 1' 2' |
| c, | $-CH_2CH_2CH_2CH_3$ 1' 2' 3' 4' |
| d, | $-CH_2CH_2OH$ 1' 2' |
| e, | $-CH_2CH_2CH_3$ 1' 2' 3' |
| f, | $-CH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_3$ 1' 2' 3' |
| g, | $-CH_2CH_2CH_2OH$ 1' 2' 3' |
| h, | $-CH_2CH_2CH_2CH_2OH$ 1' 2' 3' 4' |

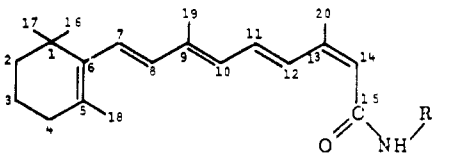
| | R |
|---|---|
| i, | $-CH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_2OH$ 1' 2'3' |
| j, |  |
| k, | $-CH_2COOCH_2CH_3$ 1' 2' 3' 4' |
| l, | $-CH_2COOH$ 1' 2' |
| m, |  |
| n, |  5'6' 7' |



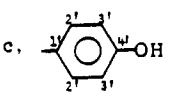
III

a, X = OH
b, X = Cl

c, X = 



IV

| | R | | R |
|---|---|---|---|
| a, | $-CH_2CH_3$ 1' 2' | d, | $-CH_2CH_2OH$ 1' 2' |
| b, | $-CH_2CH_2CH_2CH_3$ 1' 2' 3' 4' | e, | $-CH_2CH_2CH_2CH_2OH$ 1' 2' 3' 4' |
| c, |  | | |

which were synthesized as analogues of *all-trans*-retinoic acid (vitamin A acid, Ia) for long-term studies of cancer chemoprevention in animals. Only one 13-*cis*-retinamide, the primary amide (IV, R = H), had previously been described in the literature (*1*). The preparation of *all-trans*-retinamides IIa–d (*2*) and IIe (*3*) had been briefly outlined in the patent literature, but the characterization data (melting point, UV spectra) were sparse. *all-trans*-*N*-(4-Hydroxyphenyl)retinamide was originally synthesized by Gander and co-workers (*3*, *4*). Recently, the *all-trans*-retinamides IIf,g,i were reported in a patent (*5*). The *all-trans*-retinamides (II) were prepared from retinoic acid (Ia) via *all-trans*-retinoyl chloride (Ib) or 1-(*all-trans*-retinoyl)-imidazole (Ic); the 13-*cis*-retinamides (IV) were prepared from 13-*cis*-retinoic acid (IIIa) by way of either 13-*cis*-retinoyl chloride (IIIb) or 1-(13-*cis*-retinoyl)imidazole (IIIc). The details of these syntheses are being reported in a separate paper (*12*).

Most of these retinamides have high chemopreventive activity in the hamster tracheal organ assay (*6*). Several have chemopreventive activity against bladder or breast cancer in vivo (*4*, *7*, *8*), and the retinoylglycine (III) is more active than *all-trans*-retinoic acid against hyperplasia in mouse prostate organ cultures. Because of the potential importance of these compounds, detailed characterization data are reported here. These data include mass spectra, $^1H$ and $^{13}C$ NMR spectra, UV spectra, and IR spectra.

## Discussion and Results

In electron-impact mass spectra of the retinamides (II, IV) determined at a direct-probe temperature of about 20 °C, the molecular ion (M) is one of the most intense peaks in the region above *m/z* 200. Less prominent peaks correspond to the loss of a methyl group (M – $CH_3$), the 2,6,6-trimethyl-1-cyclohexenyl

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group (M – 123), or the R group (*m/z* 298, M – R, R ≠ aryl). In addition, the following prominent peaks, usually more intense than *m/z* 298 or M – $CH_3$, are observed in all of the spectra: *m/z* 282 (M – NHR – H), 267 (282 – $CH_3$), 255 (M – CONHR), 241 (M – $CH_3$ – CONHR + H), 240, 239, 225 (240 – $CH_3$), 213, 211, 201. Other prominent peaks, as well as less intense peaks, also appear in this region, and numerous strong peaks are in all of the spectra in the region below *m/z* 200. In the Experimental Section, peaks in the region above *m/z* 200 and with a relative intensity equal to or greater than that of an arbitrarily chosen reference peak (usually one of the three peaks at *m/z* 239–241) are listed.

As expected, in the 100-MHz $^1H$ NMR spectra there is little, or no, variation among the various *all-trans*-retinamides (Table I) in the chemical shifts of protons in the retinoyl group, or among the five 13-*cis*-retinamides (Table II) in the chemical shifts of the 13-*cis*-retinoyl protons. The ranges given for the chemical shifts of protons at positions 2, 3, and 4 are estimates because methyl-group peaks overlap or are superimposed on these multiplets. The absorption for the protons on C14, C18, C19, and C20 are designated singlets in the tables since they appear to be broadened singlets. All, however, can be shown by spin-decoupling experiments to be multiplets. In the all-trans amides, chemical shifts of the protons at positions 7, 8, 10, and 12 are overlapping and are sometimes overlapped by, or coincident with, the NH absorption. The signal of the C11 proton is a characteristic doublet of doublets. The major differences between the 100-MHz proton spectra of the all-trans and 13-cis amides are the pronounced downfield shift of the C12 proton signal and the upfield shifts of the C14 and C20 proton signals in the spectra of the 13-cis amides. The $^{13}C$ NMR spectra of the *all-trans*-retinamides (Table III) are in excellent agreement with one another and with data from spectra of other all-trans retinoids determined by Englert (*9*) and assigned with the use of lanthanide shift reagents. The greatest differences in the $^{13}C$ NMR spectra of the 13-*cis*-retinamides (Table IV) relative to the spectra of the trans amides are the downfield shift of C20 (ca. 7.2 ppm) and the upfield shift of C12 (5–6 ppm). Significant upfield shifts are also observed in the C13 (1.8–2 ppm), C14 (1.7–1.8 ppm), and C15 (0.4–0.5 ppm) peaks in the 13-*cis*-retinamide spectra.

The aliphatic *all-trans*-retinamides have a UV absorption maximum at 347–348 nm with a molar absorptivity ($\epsilon$) of about 50 000–51 000 L $mol^{-1}$ $cm^{-1}$ (Table V). In the spectra of the 13-*cis*-retinamides this maximum is shifted slightly (2–4 nm) to longer wavelengths, and the molar absorptivity is lower. Both the absorption maxima and the absorptivities are greater in the *N*-aryl amides.

The IR spectra of all of these retinamides (II, IV) show at least one strong band in the region 965–985 $cm^{-1}$. This band is due to the C—H out-of-plane deformation or C=C twist vibrations of the trans-disubstituted ethylene groups, $HC_7{=}C_8H$ and $HC_{11}{=}C_{12}H$ (*10*, *11*). All of the compounds with secondary amide structures show amide I and II absorptions near 1650 and 1530 $cm^{-1}$. Detailed IR data are given in the individual sections of the Experimental Section.

## Experimental Section

Ultraviolet spectra were determined with ethanol solutions, unless otherwise indicated, and were recorded with a Varian/Cary Model 17 spectrophotometer. Infrared spectra were determined from specimens in pressed potassium bromide disks and were recorded with a Perkin-Elmer Model 621 spectrophotometer or with a Nicolet Model MX-1E Fourier-transform IR spectrometer; s = strong, w = weak, sh = shoulder. IR spectra determined with the latter instrument are designated Fourier transform in the following sections. The Fourier-transform IR spectra summarized below were run at higher resolu-

Table I. $^1H$ NMR Spectral Data for *all-trans*-Retinamides (II)[a]

| compd | 16 + 17 | 18[b] | 19[c] | 20 | 2 + 3[d] | 4 | 14 | 7, 8, 10, 12[e] | 11[f] | NH[g] | other positions |
|---|---|---|---|---|---|---|---|---|---|---|---|
| IIa | 1.03 s | 1.71 s | 1.98 s | 2.35 s | 1.3–1.8 m | 1.9–2.2 m | 5.71 s | 6.0–6.4 m | 6.91 m | 5.9 t | 2.85 d, 1′ |
| IIb | 1.03 s | 1.71 s | 1.99 s | 2.37 s | 1.3–1.8 m | 1.9–2.2 m | 5.71 s | 6.0–6.4 m | 6.93 m | 5.83 t | 1.16 t, 2′; 3.34 m, 1′ |
| IIc | 1.03 s | 1.71 s | 1.99 s | 2.37 s | 1.1–1.8 m[h] | 1.8–2.2 m | 5.71 s | 6.0–6.4 m | 6.93 m | 5.84 t | 0.74–1.1 m, 4′; 1.1–1.8 m;[h] 3.3 m, 1′ |
| IId | 1.03 s | 1.71 s | 1.98 s | 2.35 s | 1.3–1.8 m | 1.9–2.2 m | 5.73 s | 6.0–6.6 m[i] | 6.93 m | 6.43 t | 3.3–3.7 m, 1′; 3.73 t, 2′ |
| IIe | 1.03 s | 1.71 s | 1.99 s | 2.36 s | 1.3–1.8[j] | 1.8–2.2 m | 5.70 s | 6.0–6.4 m | 6.93 m | 5.76 t | 0.93 t, 3′; 1.3–1.8 m;[j] 3.27 m, 1′ |
| IIf | 1.03 s | 1.71 s | 1.99 s | 2.35 s | 1.3–1.8 m | 1.9–2.2 m | 5.75 s | 6.0–6.6 m[i] | 6.93 m | 6.42 t | 1.2 d, 3′; 3.0–3.7 m, 1′; 3.63, OH; 3.94 m, 2′ |
| IIg | 1.03 s | 1.71 s | 1.98 s | 2.35 s | 1.3–1.9[j] | 1.9–2.2 m | 5.72 s | 6.0–6.6 m[i] | 6.93 m | 6.43 t | 1.3–1.9 m;[j] 3.46 m, 1′; 3.65 m, 3′; 3.94, OH |
| IIh | 1.03 s | 1.71 s | 1.99 s | 2.35 s | 1.3–1.8[h] | 1.9–2.2 m | 5.71 s | 6.0–6.4 m[i] | 6.93 m | *k* | 1.3–1.8 m;[h] 3.04, OH; 3.34 m, 1′; 3.67 m, 4′ |
| IIi | 1.03 s | 1.71 s | 1.98 s | 2.33 s | 1.3–1.8 m | 1.8–2.2 m | 5.75 s | 6.0–6.4 m | 6.93 m | 6.67 t | 3.3–4.0 m, 1′, 2′, and 3′; 4.0–4.6 m, 2 OH |
| IIj | 1.03 s | 1.72 s | 1.99 s | 2.36 s | 1.3–1.8 m | 1.8–2.2 m | 5.71 s | 6.0–6.5 m | 6.95 m | 5.91 t | 1.35 s and 1.44 s, 5′ and 6′; 3.2–3.8 m, 1′; 3.5–3.8 m and 3.9–4.2 m, 3′; 4.1–4.4 m, 2′ |
| IIk | 1.03 s | 1.71 s | 1.99 s | 2.35 s | 1.3–1.8 m | 1.9–2.2 m | 5.77 s | 6.0–6.4 m[i] | 6.95 m | *k* | 1.28 t, 4′; 4.07 d, 1′; 4.22 q, 3′ |
| III | 1.03 s | 1.72 s | 1.99 s | 2.34 s | 1.3–1.8 m | 1.9–2.2 m | 5.79 s | 6.0–6.5 m | 6.95 m | 6.53 t | 4.12 d, 1′; 9.03 s, COOH |
| IIm ($Me_2SO$-$d_6$) | 1.03 s | 1.70 s | 1.99 s | 2.36 s | 1.3–1.8 m | 1.8–2.2 m | 6.03 s | 6.1–6.6 m | 6.99 m | 9.15 s[l] | 6.6–6.8 m and 7.3–7.6 m, 2′ and 3′; 9.74 s, OH[l] |
| IIn | 1.04 s | 1.73 s | 2.00 s | 2.41 s | 1.3–1.8 m | 1.9–2.2 m | 5.80 s | 6.0–6.5 m | 6.8–7.2 m | 7.62 s | 1.36 s, 7′; 6.96 and 7.50 AA′BB′ mult, 2′ and 3′ |

[a] The numbers at the tops of the columns and the primed numbers in the last column specify the positions of the protons in the retinamides (structures IIa–n). Chemical shifts are in parts per million downfield from internal tetramethylsilane. Spectra were determined at 100 MHz with $CDCl_3$ solutions except for the spectrum of IIm, which was determined with $Me_2SO$-$d_6$ solutions; s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet. [b] Overlaps downfield side of multiplet due to protons at positions 2 and 3. [c] Superimposed on multiplet due to protons at position 4. [d] Downfield side of this multiplet estimated because of overlapping with the chemical shift of protons on C18. [e] Includes NH signal when indicated. [f] Center of doublet of doublets; partly obscured in IIn by aromatic CH. [g] Chemical shift varies because of hydrogen bonding. [h] Includes $CH_2$ protons 2′, 3′, 2, and 3. [i] Includes NH. [j] Includes $CH_2$ protons at positions 2′, 2, and 3. [k] NH is part of multiplet due to protons at positions 7, 8, 10, 12, NH. [l] The chemical shifts of NH and OH were not distinguished; the assignments listed might actually be in reverse order.

Table II. $^1$H NMR Spectral Data for 13-*cis*-Retinamides[a]

| compd | 16 + 17 | 18[b] | 19[c] | 20[c] | 2 + 3[d] | 4 | 14 | 7, 8, 10 | 11[e] | 12 | NH | other positions |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| IVa | 1.03 s | 1.71 s | 1.97 s | 2.01 s | 1.3–1.8 m | 1.9–2.2 m | 5.57 s | 6.0–6.4 m | 6.87 m | 7.84 d | 5.77 t | 1.15 t, 2′, 3.34 m, 1′ |
| IVb | 1.03 s | 1.71 s | 1.97 s | 2.01 s | 1.1–1.8 m[f] | 1.9–2.2 m | 5.57 s | 6.0–6.4 m | 6.86 m | 7.83 d | 5.76 t | 0.8–1.1 m, 4′, 1.1–1.8;[f] 3.30 m, 1′ |
| IVd | 1.03 s | 1.71 s | 1.97 s | 2.01 s | 1.3–1.8 m | 1.8–2.2 m | 5.60 s | 6.0–6.4 m | 6.89 m | 7.80 d | 6.42 t | 3.3–3.6 m, 1′; 3.6–3.8 m, 2′ and OH |
| IVe | 1.03 s | 1.71 s | 1.97 s | 2.01 s | 1.3–1.8 m[f] | 1.8–2.2 m | 5.57 s | 6.0–6.4 m[g] | 6.87 m | 7.82 d | *g* | 1.3–1.8;[f] 2.95, OH; 3.32 m, 1′; 3.66 m, 4′ |
| IVc | 1.03 s | 1.70 s | 1.99 s | 2.05 s | 1.3–1.8 m | 1.8–2.2 m | 5.88 s | 6.1–6.4 m | 6.94 m | 8.02 d | 9.14[h] | 6.6–6.8 m and 7.3–7.6 m, 2′ and 3′; 9.72, OH[h] |
| IIIc | 1.05 s | 1.73 s | 2.04 s | 2.24 s | 1.3–1.8 m | 1.9–2.2 m | *i* | 6.0–6.6 m[i] | 7.1–7.4 m | 7.81 d | | 7.1 m and 7.54 m, imidazole positions 4 and 5; 8.21 m, imidazole position 2 |

[a] The numbers at the tops of the columns and the primed numbers in the last column designate the positions of the protons in the 13-*cis*-retinamides (IVa–e). Chemical shifts are in parts per million downfield from internal tetramethylsilane. Spectra were determined at 100 MHz with $CDCl_3$ solutions except for the spectrum of IVe, which was determined with a $Me_2SO$-$d_6$ solution; s = singlet, d = doublet, t = triplet, m = multiplet. [b] Overlaps downfield side of multiplet due to protons at positions 2 and 3. [c] Superimposed on multiplet due to protons at position 4. [d] Downfield side of this multiplet estimated because of overlapping with the chemical shift of protons on C18. [e] Center of doublet of doublets; overlaps imidazole protons in III. [f] Includes protons at positions 2′, 3′, 2, 3. [g] The multiplet at δ 6.0–6.4 also includes NH. [h] The chemical shifts of NH and OH were not distinguished; the assignments listed might actually be in reverse order. [i] The multiplet at 6.0–6.6 includes protons at C14, C7, C8, C10.

tion than the spectra determined dispersively and, therefore, may include additional bands and shoulders that are merged or weak in the dispersive spectra. Mass spectral (MS) data were taken from low-resolution, electron-impact spectra determined at 70 eV with a Varian/MAT Model 311A spectrometer; the direct-probe temperature was 20 °C. M = molecular ion; some of the other peaks are identified as probable fragments, e.g., M minus a fragment. The peaks listed are those that appear above *m/z* 200 with relative intensity equal to or greater than that of an arbitrarily chosen peak, which is specified for each compound. Usually, the chosen reference peak is the least intense peak of the three-peak cluster at *m/z* 239–241. Some significant, but less intense, peaks above *m/z* 200 are also listed. Mass spectra of several different samples of most of the retinamides were determined at different times. In some cases, there are variations among several mass spectra of a compound in the relative intensities of the three peaks at *m/z* 239–241 and, also, in the number of peaks with relative intensity equal to or greater than that of the chosen reference peak; but most of the listed peaks are always more intense than the reference peak. $^1$H NMR spectra were determined at 100 MHz with a Varian XL-100-15 spectrometer. $^{13}$C NMR spectra were determined with a Varian Model XL-100-15 (25.2 MHz) or a Bruker WH-400 (100.6 MHz) spectrometer.

***all-trans*-N-Methylretinamide (*IIa*).** Mass spectrum (relative intensity ≥ that of fragment *m/z* 240), *m/z* 314 (M + 1), 313 (M), 298 (M – $CH_3$), 282 (M – $NHCH_3$ – H), 267 (282 – $CH_3$), 256, 255 (M – $CONHCH_3$), 241 (M – $CH_3$ – $CONHCH_3$ + H), 240, 239, 225 (240 – $CH_3$), 213, 211, 202, 201, 200, 190 (M – 2,6,6-trimethylcyclohexenyl); IR (4000–700 $cm^{-1}$) 3300 s, 3035, 2980 sh, 2950 sh, 2910 s, 2850, 2820, 1625 s, 1610, 1575, 1565, 1530 s, 1440, 1405, 1390 sh, 1355, 1305 w, 1270, 1265, 1200, 1155, 1120, 1070, 1030 sh, 1020, 1005, 965 s, 885, 875, 855 w, 845 w, 830 w, 820, 765, 710, 695 w.

***all-trans*-N-Ethylretinamide (*IIb*).** Mass spectrum (relative intensity ≥ that of fragment *m/z* 298), *m/z* 328 (M + 1), 327 (M), 313, 312 (M – $CH_3$), 298 (M – $C_2H_5$), 282 (M – $NHC_2H_5$ – H), 267 (282 – $CH_3$), 256, 255 (M – $CONHC_2H_5$), 241 (M – $CH_3$ – $CONHC_2H_5$ + H), 240, 239, 226, 225 (240 – $CH_3$), 214, 213, 212, 211, 206, 205, 204 (M – 2,6,6-trimethylcyclohexenyl), 203, 202, 201, 200; IR (4000–700 $cm^{-1}$) 3300 s, 3050, 2985 sh, 2960, 2930 s, 2905 sh, 2860, 2820, 1630 s, 1615 s, 1585, 1575, 1565, 1530 s, 1455, 1445, 1435, 1390, 1370 w, 1360, 1350, 1290, 1275 sh, 1270, 1200, 1160, 1150, 1130 w, 1105 w, 1065, 1035, 1025, 1005 w, 970 s, 900 sh, 890 w, 875, 860 w, 850 w, 835 w, 825, 815 sh, 790 w, 720.

***all-trans*-N-Butylretinamide (*IIc*).** Mass spectrum (relative intensity ≥ that of fragment *m/z* 239), *m/z* 356 (M + 1), 355 (M), 340 (M – $CH_3$), 282 (M – $NHC_4H_9$ – H), 267 (282 – $CH_3$), 256, 255 (M – $CONHC_4H_9$), 241 (M – $CH_3$ – $CONHC_4H_9$ + H), 240, 239, 232 (M – 2,6,6-trimethylcyclohexenyl), 225 (240 – $CH_3$), 219, 218, 213, 211, 206, 202, 201, 200 (also, *m/z* 298 (M – $C_4H_9$), less intense than *m/z* 239); IR (Fourier transform, 4000–800 $cm^{-1}$) 3340 sh, 3310 s, 3050, 3040, 2990, 2955 s, 2925 s, 2900 sh, 2865, 2845, 2825, 1630 s, 1615 s, 1585, 1575, 1565, 1545 sh, 1530 s, 1465, 1450, 1430, 1390, 1375 w, 1370 w, 1360 sh, 1355, 1315, 1300 sh, 1295 sh, 1275 sh, 1265, 1230, 1200, 1160, 1140, 1130, 1120, 1090 w, 1065 w, 1035, 1030, 1010 w, 995, 965 s, 900 w, 890, 875, 860 w, 840, 830, 820.

***all-trans*-N-(2-Hydroxyethyl)retinamide (*IId*).** Mass spectrum (relative intensity ≥ that of *m/z* 241), *m/z* 344 (M + 1), 343 (M), 328 (M – $CH_3$), 325 (M – $H_2O$), 310 (M – $CH_3$ – $H_2O$), 282 (M – $NHCH_2CH_2OH$ – H), 267 (282 – $CH_3$), 256, 255 (M – $CONHCH_2CH_2OH$), 241 (M – $CH_3$ – $CONHCH_2CH_2OH$ + H), 240, 239, 225 (240 – $CH_3$), 220 (M – 2,6,6-trimethylcyclohexenyl), 213, 211, 207, 206, 202, 201, 200 (also, *m/z* 298 (M – $CH_2CH_2OH$), less intense than *m/z* 241); IR (Fourier

Table III. $^{13}C$ NMR Spectral Data for *all-trans*-Retinamides (II)[a]

| compd | C19 | C20 | C3 | C18 | C16 + C17 | C4 | C1 | C2 | C14 |
|---|---|---|---|---|---|---|---|---|---|
| IIa | 12.86 | 13.63 | 19.36 | 21.71 | 29.01 | 33.19 | 34.35 | 39.81 | 121.68 |
| IIb | 12.84 | 13.54 | 19.26 | 21.72 | 28.97 | 33.11 | 34.26[c] | 39.66 | 121.95 |
| IIc | 12.84 | 13.54 | 19.27 | 21.72 | 28.96 | 33.10 | 34.26 | 39.65 | 121.97 |
| IId, $CDCl_3$ | 12.85 | 13.66 | 19.24 | 21.73 | 28.97 | 33.10 | 34.25 | 39.64 | 121.17 |
| $Me_2SO$-$d_6$ | 12.52 | 13.12 | 18.82 | 21.44 | 28.77 | 32.63 | 33.86 | 39.30 | 123.19 |
| IIe | 12.83 | 13.55 | 19.28 | 21.71 | 28.97 | 33.11 | 34.27 | 39.68 | 122.02 |
| IIf | 12.85 | 13.67 | 19.24 | 21.74 | 28.96 | 33.10 | 34.25 | 39.62 | 121.23 |
| IIg | 12.85 | 13.67 | 19.25 | 21.72 | 28.97 | 33.11 | 34.26 | 39.66 | 121.28 |
| IIh | 12.85 | 13.60 | 19.25 | 21.72 | 28.97 | 33.10 | 34.25 | 39.65 | 121.73 |
| IIi | 12.85 | 13.73 | 19.25 | 21.74 | 28.98 | 33.11 | 34.26 | 39.66 | 120.97 |
| IIj | 12.84 | 13.65 | 19.27 | 21.70 | 28.97 | 33.10 | 34.28 | 39.68 | 121.14 |
| IIk | 12.83 | 13.68 | 19.29 | 21.71 | 28.99 | 33.14 | 34.30 | 39.74 | 120.76 |
| III | 12.86 | 13.83 | 19.29 | 21.74 | 28.99 | 33.14 | 34.30 | 39.74 | 120.23 |
| IIm ($Me_2SO$-$d_6$) | 12.54 | 13.18 | 18.78 | 21.48 | 28.76 | 32.62 | 33.83 | 39.23 | 123.14 |
| IIn | 12.87 | 13.68 | 19.23 | 21.75 | 28.96 | 33.08 | 34.25 | 39.60 | 120.81[e] |

| compd | C7 | C11, C5, C10[b] | C12 | C8 | C6 | C9 | C13 | C15 | other C |
|---|---|---|---|---|---|---|---|---|---|
| IIa | 128.21 | 129.57, 129.69, 129.74 | 135.78 | 137.48 | 137.94 | 138.54 | 148.08 | 167.94 | 26.10, C1′ |
| IIb | 128.05 | 129.37, 129.66, 129.66 | 135.79 | 137.39 | 137.77 | 138.40 | 147.89 | 167.12 | 14.92, C2′; 34.18,[c] C1′ |
| IIc | 128.04 | 129.37, 129.68, 129.68 | 135.80 | 137.39 | 137.77 | 138.39 | 147.88 | 167.18 | 13.78, C4′; 20.20, C3′; 31.85, C2′; 39.13, C1′ |
| IId | 128.27 | 129.57, 129.77, 129.93 | 135.45 | 137.31 | 137.72 | 138.81 | 148.83 | 168.41 | 42.34, C1′; 62.05, C2′ |
| | 127.14 | 128.72, 129.11, 130.12 | 136.38 | 137.14 | 137.38 | 137.38 | 145.89 | 166.42 | 41.36, C1′; 60.11, C2′ |
| IIe | 128.05 | 129.36, 129.66, 129.66 | 135.82 | 137.40 | 137.79 | 138.36 | 147.83 | 167.23 | 11.46, C3′; 23.00, C2′; 41.13, C1′ |
| IIf | 128.26 | 129.58, 129.76, 129.90 | 135.46 | 137.32 | 137.72 | 138.79 | 148.82 | 168.35 | 20.89, C3′; 47.11, C1′; 67.39, C2′ |
| IIg | 128.24 | 129.58, 129.75, 129.81 | 135.51 | 137.32 | 137.76 | 138.73 | 148.60 | 168.39 | 32.40, C2′; 36.18, C1′; 59.33, C3′ |
| IIh | 128.15 | 129.60, 129.60, 129.72 | 135.64 | 137.33 | 137.74 | 138.57 | 148.14 | 167.60 | 26.26, C3′; 29.84, C2′; 39.17, C1′; 62.05, C4′ |
| IIi | 128.26 | 129.64, 129.77, 130.10 | 135.46 | 137.34 | 137.73 | 138.86 | 149.21 | 168.88 | 42.16, C1′; 63.89, C3′, 71.29, C2′ |
| IIj | 128.26 | 129.59, 129.74, 129.86 | 135.50 | 137.35 | 137.78 | 138.74 | 148.90 | 167.26 | 25.26 and 26.84, C5′ and C6′; 41.48, C1′; 66.88, C3′; 74.84, C2′; 109.31, C4′ |
| IIk | 128.28 | 129.66, 129.78, 130.00 | 135.58 | 137.40 | 137.84 | 138.79 | 149.39 | 167.14 | 14.14, C4′; 41.36, C1′; 61.38, C3′, 170.37, C2′ |
| III | 128.43 | 129.66, 129.86, 130.49 | 135.39 | 137.36 | 137.79 | 139.13 | 150.26 | 168.38 | 41.60, C1′; 173.14, C2′ |
| IIm | 127.35, 129.23, 130.12, 131.28[d] | | 136.18 | 137.07 | 137.29 | 137.87 | 147.37 | 164.21 | 115.06, C3′; 120.76, C2′; 153.27, C4′; C1′ (footnote *d*) |
| IIn | 128.37 | 129.60, 129.80, 130.19 | 135.48 | 137.32 | 137.72 | 139.03 | 150.26 | 165.36 | 27.14, C7′; 39.05, C6′; 121.58;[e] 136.08, C1′; 146.86, C4′; 177.60, C5′ |

[a] Chemical shifts are in parts per million downfield from internal tetramethylsilane. All spectra were determined from $CDCl_3$ solutions except for the spectrum of IIm, which was determined from $Me_2SO$-$d_6$ solutions. The second set of data for IId was also taken from a spectrum determined from a $Me_2SO$-$d_6$ solution. The data shown in this table were obtained from spectra recorded at either 25.2 or 100.6 MHz. Spectra of some of these retinamides were recorded at both 25.2 and 100.6 MHz; there were no significant differences in the data. [b] The chemical shifts ($CDCl_3$) of δ 129.36–129.66, 129.66–129.86, and 129.66–130.49 listed for C11, C5, and C10 correlate well with assignments based on the use of shift reagents (*9*), but they have not been assigned to individual positions. [c] The chemical shift (δ 34.26) assigned to C1 agrees well with the chemical shift of C1 of other derivatives in this group, but the assignment of δ 34.26 and 34.18 to C1 and C1′, respectively, has not been verified. [d] The chemical shifts of C5, C7, C10, C11, C1′ are not assigned individually. Peaks due to two of these carbon atoms coincide. [e] Chemical shifts, δ 120.81 and 121.58, of C14, C2′, and C3′ are not assigned individually. Peaks due to two of these carbon atoms coincide.

Table IV. $^{13}C$ NMR Data for 13-*cis*-Retinamides (IVa-e)[a]

| compd | C19 | C3 | C20 | C18 | C16 + C17 | C4 | C1 | C2 | C14 |
|---|---|---|---|---|---|---|---|---|---|
| IVa | 12.79 | 19.28 | 20.73 | 21.69 | 28.97 | 33.11 | 34.26[d] | 39.67 | 120.23 |
| IVb | 12.79 | 19.28 | 20.74 | 21.69 | 28.97 | 33.11 | 34.26 | 39.67 | 120.25 |
| IVd | 12.81 | 19.27 | 20.86 | 21.72 | 28.99 | 33.13 | 34.28 | 39.69 | 119.41 |
| IVe | 12.81 | 19.25 | 20.82 | 21.72 | 28.98 | 33.11 | 34.26 | 39.65 | 120.00 |
| IVc ($Me_2SO$-$d_6$) | 12.52 | 18.76 | 20.61 | 21.47 | 28.75 | 32.60 | 33.81 | 39.16 | 121.02 |

| compd | C7 | C5, C10, C11, C12[b] | C8[c] | C6[c] | C9 | C13 | C15 | other C |
|---|---|---|---|---|---|---|---|---|
| IVa | 127.77 | 129.69, 130.05, 130.38, 130.61 | 137.64 | 137.74 | 138.38 | 145.98 | 166.66 | 14.92, C2'; 34.15,[d] C1' |
| IVb | 127.76 | 129.69, 130.06, 130.37, 130.61 | 137.64 | 137.74 | 138.37 | 145.94 | 166.71 | 13.77, C4'; 20.20, C3'; 31.84, C2'; 39.14, C1' |
| IVd | 128.15 | 129.68, 129.87, 130.43, 131.01 | 137.53 | 137.74 | 138.96 | 147.10 | 167.99 | 42.41, C1'; 62.20, C2' |
| IVe | 127.93 | 129.79, 129.91, 130.51, 130.59 | 137.55 | 137.71 | 138.62 | 146.32 | 167.09 | 26.28, C3'; 29.84, C2'; 39.14, C1'; 62.07, C4' |
| IVc | 127.26 | 129.20, 130.24, 130.31, 130.60, 131.19[e] | 137.17 | 137.24 | 138.22 | 145.84 | 163.66 | 115.00, C3'; 120.69, C2'; C1';[e] 153.20, C4' |

[a] All spectra were determined with $CDCl_3$ solutions at 100.6 MHz except for the spectrum of IVc, which was determined with a $Me_2SO$-$d_6$ solution. Chemical shifts are in parts per million downfield from internal tetramethylsilane. [b] Chemical shifts in this region are due to C5, C10, C11, and C12 (*9*), but they were not assigned to individual positions. [c] The assignments shown for these two peaks are not certain and may in actuality be in the reverse order. [d] The chemical shift ($\delta$ 34.26) assigned to C1 is in excellent agreement with the chemical shift of other 1,3-*cis*- and *all-trans*-retinamides, but the assignment of $\delta$ 34.26 and 34.15 to C1 and C1', respectively, has not been verified. [e] This group of five peaks in the region $\delta$ 129-132 also includes C1'.

Table V. Ultraviolet Absorption Data[a]

| R | *all-trans*-retinamides $\lambda_{max}$ ($\epsilon$) | *all-trans*-retinamides $\lambda_{min}$ | 13-*cis*-retinamides $\lambda_{max}$ ($\epsilon$) | 13-*cis*-retinamides $\lambda_{min}$ |
|---|---|---|---|---|
| $CH_3$ | 347 (50 000) | 225-230 | | |
| $C_2H_5$ | 347 (50 200) | 225-230 | 349 (45 800)<br>242 (9400) | 260-278 |
| $C_4H_9$ | 347 (51 000) | 225-230 | 350 (45 800)<br>243 (9400) | 270 |
| $CH_2CH_2OH$ | 347 (50 700) | 225-230 | 350 (44 400)<br>242 (9600) | 262-277 |
| $C_3H_7$ | 347 (50 500) | 225-230 | | |
| $CH_2CHOHCH_3$ | 347 (51 000) | 225-230 | | |
| $CH_2CH_2CH_2OH$ | 347 (51 000) | 225-230 | | |
| $CH_2(CH_2)_2CH_2OH$ | 347 (51 000) | 225-230 | 350 (42 200)<br>242 (9200) | 275 |
| $CH_2CHOHCH_2OH$ | 347-348 (50 000) | 225-230 | | |
| $CH_2COOC_2H_5$ | 349 (49 200) | 225-230 | | |
| $CH_2COOH$ | 347 (49 400) | | | |
| $C_6H_4OH$ | 362 (56 400)<br>228-230 (11 300) | 261 | 366 (47 700)<br>240 (13 700) | 275 |
| $C_6H_4OCOC(CH_3)_3$ | 362 (59 000)<br>228-230 (15 000) | 260-265 | | |

[a] All spectra were determined with absolute ethanol solutions except for *all-trans*-*N*-(4-hydroxyphenyl)retinamide, which was determined with methanol solutions; $\lambda$ in nanometers and $\epsilon$ in L $mol^{-1}$ $cm^{-1}$.

transform, 4000–700 $cm^{-1}$) 3435 s, 3355 s, 3030, 2955, 2925 s, 2905 sh, 2865, 2850 sh, 2825, 1645 s, 1640 s, 1615, 1585 s, 1520 s, 1470 sh, 1440, 1415, 1395 w, 1370, 1360, 1340 w, 1325 w, 1310 w, 1275 sh, 1270, 1230, 1200, 1175 w, 1160, 1135 w, 1120 w, 1090, 1055, 1030, 1010 w, 985 s, 910 w, 900 w, 880, 855 w, 835, 825, 790 w, 750 w, 710 w.

***all-trans*-*N*-Propylretinamide (*IIe*).** Mass spectrum (relative intensity ≥ that of fragment *m/z* 239), *m/z* 342 (M + 1), 341 (M), 326 (M – $CH_3$), 282 (M – $NHC_3H_7$ – H), 267 (282 – $CH_3$), 256, 255 (M – $CONHC_3H_7$), 241 (M – $CH_3$ – $CONHC_3H_7$ + H), 240, 239, 225 (240 – $CH_3$), 218 (M – 2,6,6-trimethylcyclohexenyl), 213, 211, 205, 204, 202, 201, 200 (also, *m/z* 298 (M – $C_3H_7$), less intense than *m/z* 239); IR (Fourier transform, 4000–700 $cm^{-1}$) 3315 s, 3050, 3040, 2990, 2960 s, 2930 s, 2905 sh, 2870 sh, 2860, 2845 sh, 2820, 1630 s, 1615 s, 1585, 1575, 1565, 1530 s, 1455, 1450 w, 1440 w, 1430, 1390 sh, 1385, 1370 w, 1360, 1355, 1335 sh, 1315 w, 1285, 1265, 1255, 1200, 1160, 1140, 1130 w, 1120 w, 1110 w, 1080, 1065 w, 1035 w, 1025 w, 1005 w, 995 w, 970 s, 890 w, 880, 845 w, 830 w, 820, 790 w, 775, 750 w, 720, 700 w.

**(±)-*all-trans*-*N*-(2-Hydroxypropyl)retinamide (*IIf*).** Mass spectrum (relative intensity ≥ that of *m/z* 240), *m/z* 358 (M + 1), 357 (M), 342 (M – $CH_3$), 324 (M – $CH_3$ – $H_2O$), 282 (M – $NHCH_2CHOHCH_3$ – H), 267 (282 – $CH_3$), 256, 255 (M – $CONHCH_2CHOHCH_3$), 241 (M – $CH_3$ – $CONHCH_2CHOHCH_3$ + H), 240, 239, 225 (240 – $CH_3$), 221, 220, 213, 211, 203, 202, 201, 200; significant MS peaks less intense than *m/z* 240, *m/z* 339 (M – $H_2O$), 298 (M – $CH_2CHOHCH_3$), 234 (M – 2,6,6-trimethylcyclohexenyl); IR (Fourier transform, 4000–700 $cm^{-1}$) 3450 s, 3340 broad, 3045 w, 3020, 2980 sh, 2965 s, 2925 s, 2865, 2845 w, 2825, 1650 s, 1640 s, 1615, 1585, 1570, 1525 s, 1470 sh, 1455, 1445, 1435 sh, 1415, 1395 w, 1375, 1370, 1360, 1325, 1305 w, 1265, 1250 sh, 1200, 1175 w, 1155, 1135, 1115, 1095 w, 1070, 1045 w, 1030, 1010, 980 s, 930, 910 w, 900, 880, 845, 835, 825 sh, 790 w, 750 w, 730 sh, 720 w.

***all-trans*-*N*-(3-Hydroxypropyl)retinamide (*IIg*).** Mass spectrum (relative intensity ≥ that of fragment *m/z* 240), *m/z* 358 (M + 1), 357 (M), 342 (M – $CH_3$), 339 (M – $H_2O$), 324 (M – $CH_3$ – $H_2O$), 282 (M – $NH(CH_2)_3OH$ – H), 267 (282 – $CH_3$),

256, 255 (M – $CONH(CH_2)_3OH$), 241 (M – $CH_3$ – $CONH(CH_2)_3OH$ + H), 240, 239, 225 (240 – $CH_3$), 221, 220, 213, 211, 203, 202, 201 (also, *m/z* 298 (M – $(CH_2)_3OH$) and 234 (M – 2,6,6-trimethylcyclohexenyl), less intense than *m/z* 240); IR (Fourier transform, 4000–700 $cm^{-1}$) 3400, 3295 s, 3080, 3050 w, 3030 w, 3020 w, 2985 sh, 2960, 2950, 2940 sh, 2925 s, 2905, 2885, 2865, 2845 sh, 2820, 1615 s, 1600 s, 1575 s, 1545 s, 1465 sh, 1445, 1435, 1410, 1390 w, 1380, 1370 w, 1355, 1350, 1305, 1275, 1270, 1225, 1205, 1195, 1160, 1125, 1115, 1095, 1070, 1045 w, 1025, 1000, 985, 970 s, 925, 895 w, 890, 875, 835, 825, 790 w, 750, 720 w.

***all-trans-N-(4-Hydroxybutyl)retinamide (IIh).*** Mass spectrum (relative intensity ≥ that of fragment *m/z* 240), *m/z* 372 (M + 1), 371 (M), 356 (M – $CH_3$), 282 (M – $NHC_4H_9$ – H), 267 (282 – $CH_3$), 256, 255 (M – $CONH(CH_2)_4OH$), 241 (M – $CH_3$ – $CONH(CH_2)_4OH$ + H), 240, 239, 235, 234, 225 (240 – $CH_3$), 213, 211, 202, 201, 200; significant MS peaks less intense than *m/z* 240, *m/z* 340 (M – $CH_2OH$), 338 (M – $CH_3$ – $H_2O$), 298 (M – $(CH_2)_4OH$), 248 (M – 2,6,6-trimethylcyclohexenyl); IR (Fourier transform, 4000–800 $cm^{-1}$) 3305 s, 3255–3235 sh, 3045, 3015 w, 2985 sh, 2965, 2960, 2935 sh, 2925 s, 2865, 2830, 1640 s, 1610, 1585, 1575, 1550 s, 1480, 1470, 1455, 1430, 1405, 1390, 1380 w, 1375, 1360, 1315 w, 1300 w, 1285 sh, 1275, 1260, 1200, 1155, 1130 w, 1120 w, 1110, 1080, 1070, 1030, 1015 w, 1000 w, 965 s, 960, 895 sh, 890 w, 875, 860 sh, 840 w, 830, 820. These IR data are from the spectrum of a specimen of IIh with mp 111–113 °C.

A polymorphic form of IIh was also obtained, mp 95–96 °C. The solid-state IR spectrum differed from, but was similar to, that of the higher-melting form. The two forms were shown to be identical in solution by TLC, HPLC, $^1H$ NMR, and $^{13}C$ NMR.

***(±)-all-trans-N-(2,3-Dihydroxypropyl)retinamide (III).*** Mass spectrum (relative intensity ≥ that of *m/z* 240), *m/z* 374 (M + 1), 373 (M), 358 (M – $CH_3$), 340 (M – $CH_3$ – $H_2O$), 282 (M – $NHCH_2CHOHCH_2OH$ – H), 267 (282 – $CH_3$), 256, 255 (M – $CONHCH_2CHOHCH_2OH$), 241 (M – $CH_3$ – $CONHCH_2CHOHCH_2OH$ + H), 240, 239, 237, 236, 225 (240 – $CH_3$), 213, 211, 202, 201, 200; significant MS peaks less intense than *m/z* 240, *m/z* 355 (M – $H_2O$), 298 (M – $CH_2CHOHCH_2OH$), 250 (M – 2,6,6-trimethylcyclohexenyl); IR (Fourier transform, 4000–700 $cm^{-1}$) 3275 s broad, 3075, 3055, 3040 sh, 2990, 2960, 2950, 2940 sh, 2930 s, 2920 sh, 2905, 2865, 2825, 1640 s, 1610 s, 1575 s, 1555, 1490 w, 1470 sh, 1450 broad, 1400, 1380, 1360, 1335 w, 1320, 1300 w, 1275, 1265, 1225 w, 1205, 1200, 1160, 1115, 1075, 1045 s, 1005 w, 990, 965 s, 950 s, 920 w, 895 w, 885 sh, 875, 850 w, 840 w, 825, 815, 790 w, 765 w, 745, 720. These IR data are from the spectrum of a specimen of III with mp 83–85 °C. A polymorphic form was also obtained, mp 101–104 °C. The solid-state IR spectrum of this form differed from, but was similar to, that of the lower-melting form. The two forms were shown to be identical in solution by $^1H$ NMR and $^{13}C$ NMR.

***Isopropylidene Derivative (IIj) of III.*** $UV_{max}$ (ethanol) 348 nm (ε 47 500).

***all-trans-N-Retinoylglycine Ethyl Ester (IIk).*** Mass spectrum (relative intensity ≥ that of *m/z* 241), *m/z* 386 (M + 1), 385 (M), 340 (M – OEt), 283, 282 (M – $NHCH_2COOC_2H_5$ – H), 268, 267 (282 – $CH_3$), 256, 255 (M – $CONHCH_2COOEt$), 254, 249, 248, 241 (M – $CH_3$ – $CONHCH_2COOEt$ + H), 240, 239, 226, 225 (240 – $CH_3$), 213, 212, 211, 209, 204, 203, 202, 201, 200; significant MS peaks less intense than *m/z* 241, *m/z* 370 (M – $CH_3$), 324, 312, 298 (M – CHCOOEt, weak), 296, 262 (M – 2,6,6-trimethylcyclohexenyl); IR (4000–700 $cm^{-1}$) 3355 s, 3035, 3020, 2975, 2965, 2940, 2920 s, 2900 sh, 2855, 1725 s, 1655 s, 1605, 1575, 1560, 1510 s, 1475, 1445, 1435, 1400, 1390, 1365, 1350, 1290 w, 1265, 1250, 1210, 1180 s, 1150, 1125, 1100, 1060 w, 1030, 1015, 960 s, 950, 875, 870 sh, 830 sh, 825, 785 w, 765 w, 710.

***all-trans-N-Retinoylglycine (III).*** Mass spectrum (relative intensity ≥ that of *m/z* 241), *m/z* 358 (M + 1), 357 (M), 267 (282 – $CH_3$), 255 (M – $CONHCH_2COOH$), 241 (M – $CH_3$ – $CONHCH_2COOH$ + H), 240, 239, 226, 225 (240 – $CH_3$), 221, 220, 213, 211, 202, 201, 200; significant MS peaks less intense than *m/z* 241, *m/z* 342 (M – $CH_3$), 339 (M – $H_2O$), 296, 282 (M – $NHCH_2COOH$ – H), 234 (M – 2,6,6-trimethylcyclohexenyl); IR (4000–700 $cm^{-1}$) 3345 s, 3045, 3030, 2985 sh, 2950 sh, 2920 s, 2900 sh, 2855, 2815, 2720 sh, 2610 (broad), 2515, 1730, 1710 s, 1620 s, 1595 s, 1575 s, 1570 sh, 1535 s, 1460 sh, 1435, 1395, 1355, 1325, 1275 w, 1255, 1230, 1215 s, 1205 sh, 1155, 1115 w, 1035 sh, 1025, 1000 w, 985 w, 965 s, 950 s, 895 w, 880, 870, 830, 815, 785 w, 715.

***all-trans-N-(4-Hydroxyphenyl)retinamide (IIm) (3,4).*** Mass spectrum (relative intensity ≥ that of *m/z* 239), *m/z* 392 (M + 1), 391 (M), 376 (M – $CH_3$), 283, 282 (M – $NHC_6H_4OH$ – H), 268 (M – 2,6,6-trimethylcyclohexenyl), 267 (282 – $CH_3$), 256, 255 (M – $CONHC_6H_4OH$), 254, 242, 241 (M – $CH_3$ – $CONHC_6H_4OH$ + H), 240, 239, 227, 225 (240 – $CH_3$), 213, 211, 203, 202, 201, 200; IR (4000–400 $cm^{-1}$) 3325, 3300, 3145 br, 3040, 3025 sh, 2950, 2931, 2905, 2865, 2825, 2800 w sh, 2725 w, 2670 w, 2595 w, 2495 w, 1875 w, 1855 w, 1815 w, 1750 w, 1645 sh, 1632 s, 1615, 1605 sh, 1595 sh, 1579 s, 1549 s, 1515 s, 1508 s, 1470 sh, 1444 s, 1410 sh, 1395 w, 1385 w, 1370, 1360, 1350 w, 1325 sh, 1315, 1275 w, 1252, 1242 s, 1230, 1181 s, 1175 s, 1160, 1130 w, 1120 w, 1110 w, 1070 w, 1045 w, 1030 w, 1015 w, 1005 w, 995 w, 970 s, 960, 930 w, 900 w, 885 w sh, 880 w, 860 w, 830 s, 825 sh, 815, 800 w sh, 775 w sh, 755 w sh, 740 w, 710 w, 700 w, 640 w, 620 w, 720, 495 w. This compound may crystallize in several polymorphic or solvated forms. The IR data were taken from the spectrum of a typical specimen, mp 173–175 °C.

***all-trans-N-[4-(Pivaloyloxy)phenyl]retinamide (IIn).*** Mass spectrum (relative intensity ≥ that of *m/z* 239), *m/z* 476 (M + 1), 475 (M), 460 (M – $CH_3$), 352 (M – 2,6,6-trimethylcyclohexenyl), 339, 338, 287, 286, 283, 282 (M – $NHC_6H_4OCOC(CH_3)_3$), 273, 267 (282 – $CH_3$), 256, 255 (M – $CONHC_6H_4OCOC(CH_3)_3$), 241 (M – $CH_3$ – $CONHC_6H_4OCOC(CH_3)_3$ + H), 240, 239, 227, 225 (240 – $CH_3$), 213, 202, 201, 200; IR (Fourier transform, strong bands only) 3365, 3360, 2945, 1735, 1730, 1675, 1585, 1520, 1510, 1400, 1300, 1195, 1170, 1155, 1130, 965.

***1-(13-cis-Retinoyl)imidazole (IIIc).*** Mass spectrum, *m/z* 350 (M), 335 (M – $CH_3$), 282 (M – imidazole), 267 (282 – $CH_3$), 239, 211, 197; IR (strong bands in the 1700–800-$cm^{-1}$ region) 1700, 1570, 1550, 1465, 1275, 1230, 1210, 1085, 980, 970, 810.

***13-cis-N-Ethylretinamide (IVa).*** Mass spectrum (relative intensity ≥ that of fragment *m/z* 240), *m/z* 328 (M + 1), 327 (M), 312 (M – $CH_3$), 282 (M – $NHC_2H_5$ – H), 267 (282 – $CH_3$), 256, 255 (M – $CONHC_2H_5$), 241 (M – $CH_3$ – $CONHC_2H_5$ + H), 240, 239, 225 (240 – $CH_3$), 213, 211, 204 (M – 2,6,6-trimethylcyclohexenyl), 202, 201, 200 (also, 298 (M – $C_2H_5$), weaker than *m/z* 240); IR (4000–700 $cm^{-1}$) 3260 s, 3065 sh, 3055, 3025, 2980 sh, 2965, 2955, 2930, 2910 sh, 2865, 2850 sh, 2830, 1645 sh, 1625 s, 1605 s, 1585, 1560, 1545 s, 1445, 1435, 1380, 1370 sh, 1355, 1350 sh, 1335 w, 1295, 1280, 1275, 1265 s, 1250, 1205, 1180, 1155 sh, 1145, 1125 w, 1115 w, 1100 w, 1065, 1040 w, 1025, 1010 w, 975 s, 960, 900, 895, 865, 840, 820, 805, 785 w, 740, 720.

***13-cis-N-Butylretinamide (IVb).*** Mass spectrum (relative intensity ≥ that of fragment *m/z* 240), *m/z* 356 (M + 1), 355 (M), 340 (M – $CH_3$), 267 (282 – $CH_3$), 256, 255 (M – $CONHC_4H_9$), 241 (M – $CH_3$ – $CONHC_4H_9$ + H), 240, 232 (M – 2,6,6-trimethylcyclohexenyl), 225 (240 – $CH_3$), 219, 218, 213, 211, 206, 202, 201, 200; significant MS peaks weaker than *m/z* 240, *m/z* 326 (M – ethyl), 312 (M – propyl), 298 (M – butyl), 282 (M – $HNC_4H_9$ – H), 239; IR (4000–700 $cm^{-1}$) 3310

s, 3055, 3020, 2985 sh, 2955 s, 2925 s, 2860, 2825, 1630 s, 1605 s, 1585, 1560, 1540 s, 1470 sh, 1455, 1435, 1430 sh, 1380 sh, 1375, 1370 sh, 1355, 1295, 1275, 1260 s, 1245, 1220 w, 1205, 1180, 1155, 1125 w, 1120 w, 1105 w, 1080 w, 1060 w, 1040 w, 1025, 1020 sh, 1010 w, 970 s, 955, 890 w, 860, 840, 835 sh, 825 w, 785, 740, 720.

***13-cis-N-(4-Hydroxyphenyl)retinamide (IVc).*** Mass spectrum (relative intensity ≥ that of fragment *m/z* 239), *m/z* 392 (M + 1), 391 (M), 376 (M - $CH_3$), 283 (M - $NHC_6H_4OH$), 282 (M - $HNC_6H_4OH$ - H), 268 (M - 2,6,6-trimethylcyclohexenyl), 267 (282 - $CH_3$), 256, 255 (M - $CONHC_6H_4OH$), 254, 241 (M - $CH_3$ - $CONHC_6H_4OH$ + H), 240, 239, 227, 225 (240 - $CH_3$), 213, 211, 203, 202, 201, 200; IR (4000-700 $cm^{-1}$) 3305 s, 3060, 3200-3010 (broad), 2990, 2950, 2920, 2885, 2860, 2820, 1630 s, 1620 sh, 1605 s, 1590, 1565 sh, 1550 s, 1510 s, 1470 w, 1435 s, 1370 sh, 1360, 1355 sh, 1310 s, 1260, 1230 s, 1190, 1180, 1170 sh, 1125 w, 1115 w, 1105 w, 1040, 1010 w, 985, 970 s, 960, 920, 885, 860, 830 s, 805, 795, 760, 705.

***13-cis-N-(2-Hydroxyethyl)retinamide (IVd).*** Mass spectrum (relative intensity ≥ that of fragment *m/z* 241), *m/z* 344 (M + 1), 343 (M), 328 (M - $CH_3$), 325 (M - $H_2O$), 324, 310 (M - $CH_3$ - $H_2O$), 282 (M - $HNCH_2CH_2OH$ - H), 267 (282 - $CH_3$), 256, 255 (M - $CONHCH_2CH_2OH$), 241 (M - $CH_3$ - $CONHCH_2CH_2OH$ + H), 240, 239, 225 (240 - $CH_3$), 220 (M - 2,6,6-trimethylcyclohexenyl), 213, 211, 207, 206, 202, 201, 200 (also, 298 (M - $CH_2CH_2OH$), less intense than *m/z* 241); IR (4000-700 $cm^{-1}$) 3375 s, 3290 broad, 3140 broad, 3060, 3030, 2985 sh, 2940 sh, 2925 s, 2905, 2860, 2825, 1655, 1620 s, 1605, 1585 s, 1575 sh, 1560, 1550, 1520 s, 1505 sh, 1460, 1450, 1445, 1425, 1380, 1370, 1360, 1330 w, 1300, 1270, 1260 s, 1245 s, 1215, 1200, 1175, 1160, 1125, 1115 w, 1100 w, 1090, 1075, 1060 sh, 1050 s, 1040, 1025, 980 sh, 975 s, 960, 935 sh, 900 w, 895, 870, 860 sh, 840, 830, 820, 795, 735, 720 sh.

***13-cis-N-(4-Hydroxybutyl)retinamide (IVe).*** Mass spectrum (relative intensity ≥ that of fragment *m/z* 240), *m/z* 371 (M), 356 (M - $CH_3$), 282 (M - $HNC_4H_8OH$ - H), 267 (282 - $CH_3$), 255 (M - $CONHC_4H_8OH$), 241 (M - $CH_3$ - $CONHC_4H_8OH$ + H), 240, 239, 235, 234, 225 (240 - $CH_3$), 213, 211, 201; significant MS peaks less intense than *m/z* 240, *m/z* 372 (M + 1), 338 (M - $CH_3$ - $H_2O$), 298 (M - $C_4H_8OH$), 248 (M - 2,6,6-trimethylcyclohexenyl); IR (4000-900 $cm^{-1}$) 3400 broad sh, 3290 broad, 3060, 3025, 2925 s, 2860, 2820, 1630 s, 1605 s, 1580, 1560, 1530 broad, 1465 sh, 1455 sh, 1445-1430 broad, 1375, 1355, 1270, 1260, 1245, 1200, 1175 w, 1155 w, 1125 w, 1110 w, 1080 sh, 1055, 1025, 970 s.

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# Syntheses of 1-Phenyl-2-(4(1*H*)-Quinazolinylidene)ethanone and Related Ethanones

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**Eleven 1-phenyl-2-(4(1*H*)-quinazolinylidene)ethanones were synthesized by the condensation of 4-methylquinazoline and the requisite methyl benzoate ester with sodium hydride as the condensing agent. Substitutents in the 3- or 4-positions of the phenyl ring were chloro, dimethylamino, methoxy, methyl, and trifluoromethyl.**

In connection with our interest in enolizable ketones (*1*) we recently had need of some 1-phenyl-2-(4(1*H*)-quinazolinylidene)ethanones which carried substituents in the 3- or 4-position of the phenyl moiety, the substituents being chloro, dimethylamino, methoxy, methyl, and trifluoromethyl (Figure 1). The parent compound has been prepared by Higashino (*2*) and Singh et al. (*3*, *4*). Singh et al. (*3*, *4*) also prepared the 4-methoxy and 4-methyl compounds. The method of Rauch et al. (*5*) was found to be a suitable procedure to produce the requisite ketones in adequate yield.

Table I lists the 1-phenyl-2-(4(1*H*)-quinazolinylidene)-ethanones prepared as well as the melting points and yields.

**Experimental Section**

The 2-methylquinazoline was prepared by the method of Schofield and Swain (*6*). The substituted benzoic acids were

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