$EtONH_2 \cdot HCl$, 8.6 g of imidazole, and 100 ml of anhyd MeCN. Next, 6.1 g (0.03 mole) of terephthaloyl chloride was added portionwise over 0.5 hr and the stirring was continued for an additional 3 hr. The solid which formed was sepd by filtration, suspended in 200 ml of H_2O, and then refiltered. An analytically pure sample was obtained with one recrystallization from H_2O. As expected, this substance, as well as **13**, gave a negative color reaction with 1% $FeCl_3$ solution. Conversely, **11** gave a dark maroon color with this reagent.

Diacetyl Terephthalohydroxamate (16).—A mixture of 3.3 g of **2**, 20 ml of Ac_2O, and 20 ml of AcOH was heated at 100° until a negative $FeCl_3$ test was obtained (approx 1.5 hr). The solid was sepd by filtration, washed with H_2O, and then throughly vacuum dried. Recrystallization from 900 ml of MeOH produced 2.4 g of a white crystalline solid. The ir spectrum (Nujol mull) exhibited characteristic bands at 3122 (broad), 1783, and 1640 cm^{-1}.

Dibenzoyl Terephthalohydroxamate (15).—This compound was prepared by two different techniques. One involved the reaction of **2** with 2 equiv of BzCl in pyridine at ambient temperature. However, a better yield was obtained by employing the procedure of Renfrow and Hauser.[22] The disodium salt of **2** was prepared by adding the required amount of **2** to 2 equiv of NaOH in anhyd MeOH. After stirring for 0.5 hr, the solid was sepd by filtration, washed several times (Et_2O), and thoroughly vacuum dried. Next, 1.2 g (0.005 mole) of this material was suspended in 12 ml of dioxane and 1.4 g (0.01 mole) of BzCl was added. The resulting mixture was stirred rapidly at 100° for 0.5 hr. After cooling, the product was added to 100 ml of cold H_2O and the resulting solid was sepd by filtration and washed with H_2O and Et_2O. Recrystallization from dioxane yielded the desired material in analytical purity. Significant ir bands were located at 3140, 1770, and 1650 cm^{-1}.

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(22) W. B. Renfrow, Jr. and C. R. Hauser, *J. Amer. Chem. Soc.*, **59**, 2308 (1937).

Organic Fluorine Compounds. IV. Synthesis and Antifungal Properties of 2-Fluoro Fatty Acid Amides[1]

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Numerous studies on the antifungal properties of fatty acids have been carried out. These were recently summarized by Gershon and Parmegiani[2] who also reported a study on the antifungal action of 2-fluoro fatty acids as compared with nonfluorinated fatty acids. Four factors which affect the antifungal activity of these compounds are concentration, chain length, pH of the medium, and presence or absence of materials such as serum albumin in the test medium.

The results confirmed, in general, that antifungal activity of nonfluorinated fatty acids was dependent on concentration and chain length, and lowering the pH of the medium enhanced fungitoxicity. The presence of beef serum reduced the activity of the toxicant. The same generalizations held true for the fluorinated fatty acids, except that a longer chain length was required for comparable activity. Whereas, in the test system employed,[2] the nonfluorinated fatty acids were most active at chain lengths of 4–10 C atoms, the fluoro fatty acids were most active at chain lengths of 8–14 C atoms. It was also concluded that the pK_a of the fatty acids did not play an important role in their antifungal activity, since the pK_a values of 2-

(1) Part III of this series: H. Gershon, S. G. Schulman, and A. D. Spevack, *J. Med. Chem.*, **10**, 536 (1967).
(2) H. Gershon and R. Parmegiani, *ibid.*, **10**, 186 (1967).

TABLE I

ETHYL ALKYLCYANOACETATES[a]

$RCH(CN)COOC_2H_5$

I	R	Yield, %	Bp (mm), °C	$n^{25}D$	Formula[c]
e	C_5H_{11}	36	77 (0.45)	1.4277	$C_{10}H_{17}NO_2$
f	C_6H_{13}	51	99 (0.75)	1.4309	$C_{11}H_{19}NO_2$
g	C_7H_{15}[b]	38	100 (0.40)	1.4331	
h	C_8H_{17}	51	109.5 (0.25)	1.4358	$C_{13}H_{23}NO_2$
i	C_9H_{19}	76	121 (0.55)	1.4367	$C_{14}H_{25}NO_2$
j	$C_{10}H_{21}$	66	139 (0.80)	1.4384	$C_{15}H_{27}NO_2$
k	$C_{12}H_{25}$	48	165 (1.45)	1.4418	$C_{17}H_{31}NO_2$

[a] $\nu_{max}^{C\equiv N}$ 2250 cm^{-1}, $\nu_{max}^{C=O}$ 1741–1745 cm^{-1} (neat). [b] Lit. ref 6, bp 111–113° (1 mm), $n^{25}D$ 1.4337. [c] All compds except g were analyzed for C, H, N.

TABLE II

ETHYL ALKYLCYANOFLUOROACETATES[a]

$RCF(CN)COOC_2H_5$

II	R	Yield, %	Bp (mm), °C	$n^{25}D$[b]	Formula[c]
e	C_5H_{11}	53	67 (0.40)	1.4081	$C_{10}H_{16}FNO_2$
f	C_6H_{13}	56	77 (0.25)	1.4130	$C_{11}H_{18}FNO_2$
g	C_7H_{15}	24	114 (3.0)	1.4164	$C_{12}H_{20}FNO_2$
h	C_8H_{17}	58	92 (0.30)	1.4193	$C_{13}H_{22}FNO_2$
i	C_9H_{19}	50	110 (0.40)	1.4230	$C_{14}H_{24}FNO_2$
j	$C_{10}H_{21}$	30	138 (1.7)	1.4257	$C_{15}H_{26}FNO_2$
k	$C_{12}H_{25}$	36	164 (2.6)	1.4302	$C_{17}H_{30}FNO_2$

[a] $\nu_{max}^{C\equiv N}$ 2250 cm^{-1}, $\nu_{max}^{C=O}$ doublet 1775–1785 and 1750–1760 cm^{-1} (neat). [b] The refractive index must be taken fairly rapidly, since exposure of the compound to the Na light causes a series of color changes which range from yellow to orange, to red and eventually to black. The nonfluorinated analogs do not undergo this reaction. [c] All compounds were analyzed for C, H, F, N.

TABLE III

2-FLUORO FATTY ACID AMIDES[a]

$RCHFCONH_2$

IV	R	Method of preparation	Yield, %	Mp, °C[b]	Formula[c]
a	CH_3	1	85	70–71	C_3H_6FNO
b	C_2H_5	1	83	76.5–77.5	C_4H_8FNO
c	C_3H_7	1	92	73–74	$C_5H_{10}FNO$
d	C_4H_9	1	99	85.5–86.5	$C_6H_{12}FNO$
e	C_5H_{11}	1	49	88–89	$C_7H_{14}FNO$
f	C_6H_{13}	1	69	93.5–94.5	$C_8H_{16}FNO$
g	C_7H_{15}	1	84	95–95.5	$C_9H_{18}FNO$
h	C_8H_{17}	1	62	98–99	$C_{10}H_{20}FNO$
i	C_9H_{19}	1	56	97–98	$C_{11}H_{22}FNO$
j	$C_{10}H_{21}$	1	11	104–105	$C_{12}H_{24}FNO$
k	$C_{12}H_{25}$	1	87	106–107	$C_{14}H_{28}FNO$
l	$C_{14}H_{29}$	2	86	92.5–94	$C_{16}H_{32}FNO$
m	$C_{16}H_{33}$	2	99	105.5–106.5	$C_{18}H_{36}FNO$

[a] $\nu_{max}^{C=O}$ 1653–1668 cm^{-1} (KBr). [b] All samples were recrystallized (Et_2O). [c] See Table II, footnote *c*.

TABLE IV
ANTIFUNGAL ACTIVITY OF FATTY ACID AMIDES AND 2-FLUORO FATTY ACID AMIDES AT pH 5.6 AND pH 4.0 IN SABOURAUD DEXTROSE AGAR AFTER 5 DAYS AT 28°

RCH_2CONH_2

	Levels of inhibition at pH 5.6[a]				Levels of inhibition at pH 4.0			
R	*A. niger*	*T. viride*	*M. corymbifera*	Antifungal spectrum index[b]	*A. niger*	*T. viride*	*M. corymbifera*	Antifungal spectrum index[b]
C_2H_5[c]	0	0	1	1	0	0	1	1
C_3H_7	1	1	1	9	1	1	1	9
C_4H_9	1	1	1	9	1	1	1	9
C_5H_{11}	1	1	2	12	1	1	2	12
C_6H_{13}	2	2	2	18	2	2	2	18
C_7H_{15}	2	2	3	21	2	2	3	21
C_8H_{17}	0	0	1	1	0	0	2	2
C_9H_{19}	0	0	0	0	0	0	1	1
$C_{10}H_{21}$	0	0	2	2	0	0	2	2
				$RCHFCONH_2$				
C_2H_5	0	0	1	1	0	0	1	1
C_3H_7	1	1	1	9	1	1	1	9
C_4H_9	1	1	1	9	1	1	1	9
C_5H_{11}	1	2	2	15	1	1	2	12
C_6H_{13}	1	2	2	15	2	2	2	18
C_7H_{15}	1	1	3	15	1	1	3	15
C_8H_{17}	0	1	1	4	0	1	2	6
C_9H_{19}	0	1	1	4	0	0	2	2
$C_{10}H_{21}$	0	1	1	4	0	1	2	6
$C_{12}H_{25}$	0	1	2	6	0	1	3	8
$C_{14}H_{29}$	0	0	1	1	0	0	1	1
$C_{16}H_{33}$	0	0	1	1	0	0	1	1

[a] Compounds incorporated in test medium at 10^4, 10^3, and 10^2 μg/ml; 3 = inhibition at all levels of compound; 2 = inhibition at two highest levels, 1 = inhibition at highest level only. [b] Antifungal spectrum index = total number of levels of inhibition multiplied by number of organisms inhibited. [c] The compounds of the nonfluorinated series where R = H, CH_3, $C_{12}H_{25}$, $C_{14}H_{29}$, and $C_{16}H_{33}$ and those of the 2-fluoro series where R = H and CH_3 were tested and found to be completely inactive.

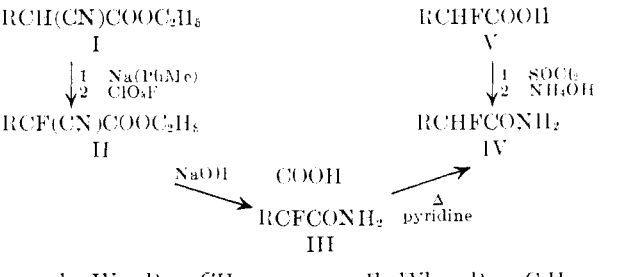
fluoro fatty acids are about 2 units lower than those of the nonfluorinated acids.

It would be of interest to determine whether the intact CO_2H is necessary for antifugal activity. Also, further study of the pH effect of the medium was desired, in order to ascertain whether the increased antifungal effect due to the lower pH resulted primarily from repression of ionization of the carboxyl function with concomitant enhanced penetration of the membranes of the test organisms. In order to gain some insight in this area, a systematic study of the fungitoxicity of aliphatic fatty acid amides was undertaken because the $CONH_2$ group is a nonionizing function which is sterically not greatly different from CO_2H.

It was stated by Goodman and Gilman[3] that amides retain considerable antifungal activity but are less active than the corresponding acids. A further search of the literature revealed only one case of the comparison of the antifungal activity of a fatty acid with its amide. Wyss, *et al.*,[4] reported that 10-undecenoamide was only slightly less active against *Trichophyton interdigitale* than the corresponding acid.

The nonfluorinated aliphatic carboxamides employed in this study are all known and were either purchased or were prepared by amination of the commercially available acid chlorides with NH_4OH. For comparison, the 2-fluoro fatty acid amides were prepared by fluorinating the Na salts of alkylated ethyl cyanoacetates in dry PhMe by means of perchloryl fluoride, followed by simultaneous saponification of the ester and hydration of the nitrile to amide.[1] These amides were then decarboxylated in boiling pyridine to yield the 2-fluoro fatty acid amides. An alternative method was to treat the 2-fluoro fatty acid with $SOCl_2$ and subsequently with NH_4OH as shown in Scheme I. The starting cyano esters (I) were prepared by

SCHEME I



Ia–IVa, R = CH_3
Ib–IVb, R = C_2H_5
Ic–IVc, R = C_3H_7
Id–IVd, R = C_4H_9
Ie–IVe, R = C_5H_{11}
If–IVf, R = C_6H_{13}
Ig–IVg, R = C_7H_{15}
Ih–IVh, R = C_8H_{17}
Ii–IVi, R = C_9H_{19}
Ij–IVj, R = $C_{10}H_{21}$
Ik–IVk, R = $C_{12}H_{25}$
IVl–Vl, R = $C_{14}H_{29}$
IVm–Vm, R = $C_{16}H_{33}$

published methods: Ia[5] and Ib–d.[6] Ie–k, although previously unknown, were also prepared by the method of Alexander and Cope.[6] Compounds IIa–IIId were known[1] and IIe–IIIk were prepared in the same manner.[1] Compounds IIIe–k were obtained as crude prod-

(3) L. S. Goodman and A. Gilman, "The Pharmacological Basis of Therapeutics," The Macmillan Co., New York, N. Y., 2nd ed, 1958, p 1092.
(4) O. Wyss, B. J. Ludwig, and R. R. Joiner, *Arch. Biochem.*, **7**, 415 (1945).
(5) M. A. Pollack, *J. Amer. Chem. Soc.*, **65**, 1335 (1943).
(6) E. R. Alexander and A. C. Cope, *ibid.*, **66**, 886 (1944).

ucts and were used in the next step without further purification. On decarboxylating IIIa–k in boiling pyridine, IVa–k were obtained. For the preparation of IVl,m the free acids, Vl,m,[2] were treated with $SOCl_2$ and then converted into the amides with NH_4OH. The pertinent data on the ethyl alkylcyanoacetates (I), ethyl alkylfluorocyanoacetates (II), and 2-fluoro fatty acid amides (IV) are contained in Tables I–III, respectively.

The fluorinated fatty acid amides along with fluoroacetamide were screened in parallel with the corresponding nonfluorinated fatty amides, against 3 fungi, *Aspergillus niger*, *Trichoderma viride*, and *Myrothecium verrucaria*, in Sabouraud dextrose agar (Difco) at pH 5.6 and pH 4.0 according to the method of Gershon and Parmegiani.[2] The results were weighted by calculating the antifungal spectrum index which is defined as the total number of levels of complete inhibition multiplied by the number of organisms inhibited within the defined system.[7,8] The antifungal results on the nonfluorinated and 2-fluorinated fatty acid amides are summarized in Table IV.

The data show that the activity of nonfluorinated and 2-fluoro fatty acid amides depends on concentration and chain length, but is not dependent on the pH of the medium. The antifungal spectral indices show clearly that the greatest activity is reached at chain lengths of 5–9 C atoms for both series of compounds. Although there is no outstanding difference in activity between the fluoro fatty acids[2] and their corresponding amides at pH 5.6, at pH 4.0 the fatty acids[2] are markedly more fungitoxic than the amides, in this test system. It appears, therefore, that the pH effect is not concerned with the medium or the test organism but with the degree of ionization of the toxicant.

The effect of the adsorbent, serum albumin, on antifungal activity of test compounds on *Trichophyton mentagrophytes* was demonstrated by adding 10% beef (Difco) to the medium at pH values of 5.6 and 7.0. The antifungal results obtained with and without beef serum are listed in Table V. The fluorinated amides were more fungitoxic against *T. mentagrophytes* at pH 5.6, than at pH 7.0, whereas the nonfluorinated amides were about equally fungitoxic, and beef serum had a deactivating effect against both sets of compounds; however, the effect was greater against the fluoro amides. These generalizations nearly parallel those describing the fatty acids.[2]

TABLE V

COMPARISON OF ANTIFUNGAL ACTIVITY OF SELECTED 2-FLUORINATED WITH NONFLUORINATED FATTY ACID AMIDES AGAINST *T. mentagrophytes* AT PH 5.6 AND 7.0 IN SABOURAUD DEXTROSE AGAR IN THE PRESENCE AND ABSENCE OF BEEF SERUM AFTER 5 DAYS AT 28°

	Levels of inhibition[a]			
	pH 5.6		pH 7.0	
	−serum	+serum	−serum	+serum
	RCH_2CONH_2			
C_4H_9	1	1	1	1
C_5H_{11}	2	2	2	2
C_6H_{13}	3	2	2	2
C_7H_{15}	3	3	3	2
C_8H_{17}	3	2	3	3
$C_{10}H_{21}$	3	2	3	2
$C_{12}H_{25}$	2	0	2	0
	$RCHFCONH_2$			
C_4H_9	3	2	2	2
C_5H_{11}	3	2	3	2
C_6H_{13}	3	2	3	2
C_7H_{15}	3	2	2	1
C_8H_{17}	3	1	2	1
$C_{10}H_{21}$	3	1	2	2
$C_{12}H_{25}$	3	2	3	2

[a] Compounds incorporated in test medium at 10^4, 10^3, and 10^2 μg/ml; 3 = inhibition at all levels of compound, 2 = inhibition at two highest levels, 1 = inhibition at highest level only.

Experimental Section[9]

Ethyl 2-Cyanoundecanoate (Id).—A mixture of nonanal (100 g, 0.70 mole), ethyl cyanoacetate (71.2 g, 0.63 mole), NH_4OAc (4.9 g, 0.063 mole), and 1.3 g of Pd–C (10%) catalyst was prepared in 100 ml of EtOH and shaken at 2 to 3 atm of H_2. Upon completion of H_2 uptake, the catalyst was removed by filtration and 150 ml of C_6H_6 was added to the filtrate. The solution was washed twice with 150-ml portions of 10% aq NaCl and 3 times with 75 ml of H_2O, and the washings were extracted twice with 50-ml portions of C_6H_6. The combined C_6H_6 solutions were freed of solvent by vacuum flash evaporation and the residue was vacuum distilled through a Vigreux column. The fraction boiling at 120–125° (0.7 mm) was collected.

Ethyl 2-Cyano-2-fluoroundecanoate (IIi).—Na dispersion (9.3 g of Na, 0.41 g-atom) was suspended in 400 ml of dry PhMe. Compound Ii (98.5 g, 0.403 mole) was added to the stirred suspension at such a rate as to keep the temperature below 90°. After completion of addition of the ester, the system was purged with dry N_2 and kept at 10–15° by external cooling. A rapid stream of perchloryl fluoride[10] was added, and upon completion of the reaction, as evidenced by cessation of heat evolution and the neutral pH of the mixture, the system was again purged with dry N_2. The suspension in PhMe was washed free of inorganic salts with several volumes of H_2O, and PhMe was removed by flash evaporation. The residue was vacuum distilled, and the product was collected at 148–152° (5 mm).

2-Fluoro-2-nonylmalonamic Acid (IIIi).—A mixture was prepared containing IIi (51.4 g, 0.2 mole), NaOH (8.8 g, 0.22 mole), 100 ml of H_2O, and 20 ml of MeOH. Stirring was continued overnight, after which the solution was adjusted to pH 2 with concd HCl and refrigerated overnight. The oily precipitate that formed was recovered by Et_2O extraction followed by removal of Et_2O. The product was used in the next step without further purification.

Method 1. 2-Fluoroundecanoamide (IVi).—Compound IIIi (6 g) was heated under reflux in 50 ml of pyridine overnight. The solvent was removed by flash evaporation, and the residue was stirred with concd aq NH_3 for 6 hr. The mixture was cooled at 4° overnight and the product was obtained by filtration, washing (H_2O), and drying at 70° (vac).

Method 2. 2-Fluoropalmitamide (IVl). 2-Fluoropalmitic acid[2] was heated under reflux with 50 ml of $SOCl_2$ overnight. Excess $SOCl_2$ was evaporated off and the residue was treated with 100 ml of NH_4OH with cooling and stirring. The product was removed by filtration, washed free of NH_3 with H_2O, and dried at 70° (vac).

(7) H. Gershon and R. Parmegiani, *Appl. Microbiol.*, **10**, 348 (1962).

(8) H. Gershon, R. Parmegiani, and W. J. Nickerson, *ibid.*, **10**, 556 (1962).

(9) Melting points were taken in a Mel-Temp melting point apparatus and are uncorrected. Ir spectra were obtained with a Perkin-Elmer Model 221 spectrophotometer, and refractive indices in a Bausch and Lomb Abbe-3L refractometer. The synthetic procedures are general, and all of the aldehydes employed in the reductive alkylation reaction were commercially available.

(10) From Pennwalt Chemical Corp., Philadelphia, Pa.; see technical pamphlet DC-1819, "Perchloryl Fluoride," on details of safety and handling.