drate (3.73 g, 20.0 mmoles). The resulting red soln was stirred under N_2 at room temperature for 72 hr, then refluxed for 1 hr. After treatment with charcoal the soln was evapd *in vacuo* to give a dark gummy residue that was dissd in H_2O (300 ml) containing concd HCl (5 ml). The resulting soln was warmed, treated with charcoal, and filtered through Celite. The orange filtrate was adjusted to pH 11 with 50% NaOH and extracted with $CHCl_3$ (3 × 150 ml). The combined extract was washed with H_2O, dried (Na_2SO_4), and evapd to dryness. An EtOH soln (100 ml) of the residue was acidified with 3 *N* ethanolic HCl (10 ml) and dild with Et_2O (300 ml). After vigorous stirring for several hours, an orange powder deposited slowly. The mixture was dild to 1 l. with Et_2O and filtered under N_2. The orange powder was recrystd under the same conditions to give a hygroscopic orange solid that was collected by filtration and dried *in vacuo* over P_2O_5 at 78°: yield 3.85 g (46%): mp sintering and gradual decpn 220–230° (Mel-Temp); λ_{max} nm ($\epsilon \times 10^{-3}$), pH 7, 243 (27.4), 293 (21.4), 338 (12.6), 385 (10.0); pmr (8% DMSO-d_6 w/v), δ 1.28 (m, 9, CH_3), 1.82 (m, 4, CH_2), 3.05 (m, 6, CH_2N), 4.24 (m, 1, CHN), 7.22 (d, 1, 7-CH), 8.04 (q, C_6H_4), 8.55 (6-CH), 9.57 (NH), 9.63 (2-CH). *Anal.* ($C_{22}H_{28}ClN_5 \cdot 2HCl \cdot H_2O$) C, H, Cl, N.

Acknowledgments.—The authors are indebted to Dr. W. C. Coburn, Jr., and members of the Molecular Spectroscopy Section of Southern Research Institute who performed most of the microanalytical and spectral determinations reported.

Hydroxylamine Derivatives as Potential Antimalarial Agents. 1. Hydroxamic Acids[1]

JOHN B. HYNES

Department of Pharmaceutical Chemistry, College of Pharmacy, Medical University of South Carolina, Charleston, South Carolina 29401

Received May 1, 1970

Hydroxamic acids have been found to exert a number of diverse pharmacologic actions including antituberculous, antifungal, and antileukemic activities.[2] In addition, certain arylhydroxamic acids inhibit nucleic acid biosynthesis *in vitro*.[3-5] Since the quinoline type antimalarials such as chloroquine, quinacrine, and quinine have been reported to function at least in part by blocking enzymatic synthesis of DNA and RNA,[6] a series of hydroxamic acids was synthesized and evaluated as a potential new class of antimalarial drugs.

A total of 33 mono- and dihydroxamic acids and related compounds was prepared and tested for *in vivo* antimalarial activity against *Plasmodium berghei* in mice.[7,8] Pertinent physical and chemical data for new compounds or those for which the melting points were significantly different from the literature values are summarized in Table I. The preparation and properties of other compounds have been described earlier.

Of the compounds tested, two showed an increase in mean survival time of infected mice of greater than 100%. They were terephthalohydroxamic acid (**2**) and dibenzoylterephthalohydroxamate (**15**) and the pertinent testing data for them are summarized in Table II. The most probable structure of **15** is based upon ir data.

p-HONHCOC$_6$H$_4$CONHOH
2

p-C$_6$H$_5$COONHCOC$_6$H$_4$CONHOCOC$_6$H$_5$
15

The similar level of activity of these two compounds suggests that **15** is enzymatically converted into **2**. However, the lack of activity of the diacetyl derivative **14** is difficult to explain on this basis.

All of the derivatives of **2** involving ring substitution, **4**, **5**, **6**, and **7**, were inactive with the exception of the tetrafluoro analog **3** which was slightly active (Δ = 2 days at 640 mg/kg). Similarly, alkylation of the hydroxamic acid portion of the molecule (**11**, **12**, and **13**) resulted in inactive compounds.

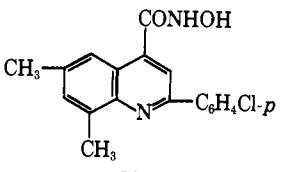
Compounds **8**, **10**, and **20** as well as adipohydroxamic acid[9] were prepared in order to evaluate the effect of altering the distance separating the two hydroxamic acid functions. Since none of these showed appreciable activity, one may conclude that this value is extremely critical.

The pyridine analog of **2**, 2,5-pyridinedicarbohydroxamic acid (**16**), as well as its 3-position isomers, **17**, **18**, and **19**, were also prepared and evaluated for antimalarial activity. As would be expected from the inactivity of **8**, only **16** showed appreciable activity but was also toxic.[10]

In addition to 4-carboxybenzohydroxamic acid (**1**) two related compounds, terephthaldihydrazide[11] and terephthaldioxime,[12] were also prepared and found to be devoid of activity.

A series of 4-substituted benzohydroxamic acids [p-XC$_6$H$_4$CONHOH (X = SO_2NH_2, NO_2, Br, Cl, I)] was prepared as described in the literature.[5,13] Only the 4-Br derivative showed appreciable activity (Δ = 3.1 days at 640 mg/kg). In addition, 3,4,5-trimethoxy-, 2-bromo-3,4,5-trimethoxy-, 2-hydroxy-3,4,5-trimethoxy-, and 3,5-dichlorobenzohydroxamic acids as well as 3,4,5-trimethoxyphenylacetohydroxamic acid were prepared as described earlier[5] and found to be inactive.

Compound **21** was synthesized as an analog of the highly potent antimalarials, the quinoline methanols.[14] It was also inactive.



21

(1) This work was supported by the U. S. Army Research and Development Command, Contract No's. DADA17-67-C-7055 and DADA17-69-C-9066.

(2) R. T. Coutts, *Can. J. Pharm. Sci.*, **2**, 1 (1967).

(3) G. R. Gale, *Proc. Soc. Exp. Biol. Med.*, **122**, 1236 (1966).

(4) G. R. Gale and J. B. Hynes, *J. Med. Chem.*, **11**, 191 (1968).

(5) G. R. Gale, J. B. Hynes, and A. B. Smith, *ibid.*, **13**, 571 (1970).

(6) L. G. Hunsicker, *Arch. Int. Med.*, **123**, 645 (1969).

(7) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

(8) Testing was carried out by Dr. L. Rane of the University of Miami.

(9) M. E. Cupery, U.S. Patent No. 2,346,665 (1944).

(10) At 640 mg/kg 2 mice died on day 4 (mean survival time for controls was 6.1 days). Deaths due to toxicity of drugs occur in 3–5 days.

(11) E. Davidis, *J. Prakt. Chem.*, **54**, 81 (1896).

(12) L. A. Errede and S. L. Hopwood, *J. Amer. Chem. Soc.*, **79**, 6507 (1957).

(13) C. H. Andrews, H. King, and J. Walker, *Proc. Roy. Soc., Ser. B*, **133**, 20 (1946).

(14) E. R. Atkinson and A. J. Puttick, *J. Med. Chem.*, **11**, 1223 (1968).

TABLE I

Name	No.	Mp, °C	Formula	Analyses[a]	Yield, %	Recrystallization medium and no.
4-Carboxybenzohydroxamic acid	1	*b*	$C_8H_7NO_4$	C, H, N	55	H_2O (1)
Terephthalohydroxamic acid	2	236 dec	$C_8H_8N_2O_4$	C, H, N	44	H_2O (1)
Tetrafluoro	3	210 dec	$C_8H_4F_4N_2O_4 \cdot H_2O$	C, H, N, F	39	H_2O (2)
2,5-Dimethyl	4	*b*	$C_{10}H_{12}N_2O_4$	C, H, N[d]	29	MeOH–H_2O 1:1 (1)
Bromo	5	212–214.5 dec	$C_8H_7BrN_2O_4$	C, H, N, Br	44	H_2O (1)
2,5-Dichloro	6	254–256 dec	$C_8H_6Cl_2N_2O_4$	C, H, N, Cl	38	H_2O (1)
Amino	7	210 dec	$C_8H_9N_3O_4 \cdot 2H_2O$	C, H, N, H_2O[e]	32	H_2O (3)
Isophthalohydroxamic acid	8	232–233[f]	$C_8H_8N_2O_4$	C, H, N	45	H_2O (1)
Trimesohydroxamic acid	9	290 dec	$C_9H_9N_3O_6$	C, H, N	31	H_2O (1)
p-Benzenediacetohydroxamic acid	10	221–223 dec	$C_{10}H_{12}N_2O_4$	C, H, N	47	H_2O (1)
N,N'-Dimethylterephthalohydroxamate	11	204–207	$C_{10}H_{12}N_2O_4$	C, H, N	27	EtOH–H_2O 4:1 (1)
O,O'-Diethyl terephthalohydroxamate	12	243–245	$C_{12}H_{16}N_2O_4$	C, H, N	33	H_2O (1)
O,O'-Dimethyl terephthalohydroxamate	13	246–247	$C_{10}H_{12}N_2O_4 \cdot 2H_2O$	C, H, N, H_2O[g]	25	H_2O (2)
Diacetyl terephthalohydroxamate	14	220 dec	$C_{12}H_{12}N_2O_6$	C, H, N	51	MeOH (1)
Dibenzoyl terephthalohydroxamate	15	235 dec[h]	$C_{22}H_{16}N_2O_6$	C, H, N	50	dioxane (1)
2,5-Pyridinedicarbohydroxamic acid	16	212 dec[i]	$C_7H_7N_3O_4$	C, H, N	36	H_2O (1)
2,4-Pyridinedicarbohydroxamic acid	17	185–186	$C_7H_7N_3O_4$	C, H, N	64	H_2O (1)
3,5-Pyridinedicarbohydroxamic acid	18	205–207 dec	$C_7H_7N_3O_4 \cdot H_2O$	C, H, N, H_2O[j]	43	H_2O (1)
2,6-Pyridinedicarbohydroxamic acid	19	233–235 dec[k]	$C_7H_7N_3O_4$	C, H, N	80	H_2O (1)
Sodium hydrogen glutarodihydroxamate[l]	20	240 dec	$C_5H_9N_2NaO_4 \cdot 2H_2O$	C, H, N, Na	34	MeOH–H_2O 4:1 (1)
2-(4-Chlorophenyl)-6,8-dimethylcinchoninohydroxamic acid	21	185–187	$C_{18}H_{15}N_2ClO_2$	C, H, N, Cl	33	MeOH–H_2O[m] (1)

[a] Where analyses are indicated only by symbols of the elements, the results were within ±0.4% of the theoretical values. The analyses were performed by Galbraith Laboratories, Knoxville, Tenn. [b] Sample did not change on heating to 300°. [c] W. Lossen [*Justus Liebigs Ann. Chem.*, **281**, 169 (1894)] reported mp 232° dec. [d] N: calcd, 12.49; found, 12.02. [e] Percentage weight loss on vacuum drying at 100°: calcd, 14.58; found, 15.09. [f] W. Lossen [*Justus Liebigs Ann. Chem.*, **281**, 169 (1894)] reported mp 192° dec. [g] Percentage weight loss on vacuum drying at 150°: calcd, 13.85; found, 14.23. [h] W. Lossen [*Justus Liebigs Ann. Chem.*, **281**, 169 (1894)] reported mp 198. [i] B. E. Hackley, Jr., R. Plapinger, M. Stolberg, and T. Wagner-Jauregg [*J. Amer. Chem. Soc.*, **77**, 3651 (1955)] reported mp 215° dec. [j] Percentage weight loss on vacuum drying at 150°: calcd, 8.37; found, 7.86. Elemental values determined for dried sample. [k] B. E. Hackley, Jr., *et al.* (see *i*) reported mp 217°. [l] G. Zvilichovsky [*J. Org. Chem.*, **34**, 486 (1969)] obtained the monopotassium salt of malonohydroxamic acid even though excess KOH was employed. [m] Reprecipitated from MeOH by adding an equal vol of H_2O.

TABLE II

Compd	Dose, mg/kg	Mean survival time, days[a]	Δ survival time, days	Mortality	Remarks
2	20	6.4	0.2	5/5	
	40	7.4	1.2	5/5	
	80	8.4	2.2	5/5	
	160	10.8	4.6	5/5	
	320	10.3[b]	4.1[b]	3/5	2 mice survived 60 days
	640	14.0[b]	6.2[b]	3/5	2 mice survived 60 days
15	20	6.4	0.3	5/5	
	40	6.4	0.3	5/5	
	80	6.4	0.3	5/5	
	160	7.6	1.5	5/5	
	320	12.4	6.3	5/5	
	640	16.6	10.5	5/5	

[a] Mean survival time of controls: 6.2 for **2**, 6.1 for **15**; mice which survive for 60 days are considered cured. [b] Data for uncured mice.

Experimental Section[15]

Unsubstituted Hydroxamic Acids.—Each of these compounds was synthesized from its corresponding Me or Et ester, which in the case of **1** (monobutyl ester), **2, 7, 8, 9, 17,** and **20** was obtained from commercial sources. Dimethyl tetrafluoroterephthalate was prepared in 68% yield from the corresponding acid by refluxing in MeOH saturated with anhyd HCl for 14 hr. The white crystalline solid melted at 78–80° (lit.[16] mp 79–80°). Dimethyl 2,5-dimethylterephthalate was obtained in 78% yield by refluxing a mixture of 2,5-dimethylterephthalic acid in MeOH in the presence of concd H_2SO_4 for 9 hr. The ester melted at 113–114.5° (lit.[17] mp 114°). Dimethyl bromoterephthalate was obtained by the HCl-catalyzed esterification of the corresponding acid, mp 53–54.5° (lit.[17] mp 57°). The preparation of dimethyl 2,5-dichloroterephthalate was also conducted using HCl as the catalyst rather than H_2SO_4 as described in the literature. Recrystallization from a large volume of MeOH yielded the desired compound in 77% yield, mp 137–138.5° (lit.[17] mp 137°, yield 50%). The dimethyl esters of 2,5- 3,5-, and 2,6-pyridinedicarboxylic acids were prepared by the H_2SO_4-catalyzed esterification technique. The melting points were resp 166–167° (lit.[18] mp 161–163°), 84.5–85.5° (lit.[19] mp 83–84°), and 123–125° (lit.[20] mp 121°). Methyl 2-(4-chlorophenyl)-6,8-dimethylcinchoninate, mp 147–149°, was supplied by Walter Reed Army Institute of Research.

The syntheses of hydroxamic acids **3, 4, 5, 6, 7, 9, 10, 16, 17, 18,** and **19** all were carried out using MeOH as the solvent and both NaOH and $NH_2OH \cdot HCl$ in excess of the theoretical amounts required to produce the disodium salt of the corresponding dihydroxamic acid. The reactions were conducted at room temperature for periods of 2–5 days. Compounds **2** and **8** were prepared in the same manner as above except that the solvent was EtOH–H_2O while **1** was prepared in MeOH–H_2O. Compounds **20** and **21** were prepared using excess NH_2OH in MeOH with MeONa as the base. In the latter case, Et_2O was added to the reaction mixture to improve the solubility of the ester.

N- and O-Alkylated Hydroxamic Acids.—Compounds **11, 12,** and **13** were prepared from their corresponding hydroxylamine hydrochlorides by a modification of the method of Koenig and Deinzer.[21] The following description of the preparation of *O,O'*-diethylterephthalohydroxamate is representative of this technique. In a system provided with a N_2 purge were placed 6.4 g of

(15) Melting points (uncor) were taken on a Fisher-Johns melting point apparatus. The ir spectra were determined using a Beckman IR 8 spectrophotometer.

(16) B. Gething, C. R. Patrick, and J. C. Tatlow, *J. Chem. Soc.*, 1574, (1961).

(17) M. Cachia and H. Wahl, *Bull. Soc. Chim. Fr.*, 1418 (1958).

(18) T. O. Soine, *J. Amer. Pharm. Ass.*, **33**, 223 (1944).

(19) J. Kuthan, Czechoslovakian Patent 109,895 (1964).

(20) H. Anderson and T. O. Soine, *J. Amer. Pharm. Ass.*, **39**, 460 (1950).

(21) T. Koenig and M. Deinzer, *J. Amer. Chem. Soc.*, **90**, 7014 (1968).

$EtONH_2 \cdot HCl$, 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}.

Acknowledgment.—The author wishes to express his gratitude to Dr. Edgar A. Steck for many helpful suggestions and discussions during the course of this work. The technical assistance of Mrs. Linda G. Hack was invaluable.

(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]

HERMAN GERSHON, RAYMOND L. RODIN, RAULO PARMEGIANI, AND PATRICIA K. GODFREY

Boyce Thompson Institute for Plant Research, Inc., Yonkers, New York 10701

Received January 28, 1970

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.