


TABLE I
 POLYMETHYLENE- α,ω -BIS-TERTIARYAMINOACETYLAMIDES AND THEIR QUATERNARY AMMONIUM SALTS

$$\begin{array}{c} \text{R}_2\text{N}^+ \text{---} \text{CH}_2\text{CONH}(\text{CH}_2)_n\text{NHCOC} \begin{array}{c} \text{+} \\ \text{NR}_2 \\ \text{X}^- \end{array} \\ \begin{array}{c} \text{R}' \\ \text{X}^- \end{array} \end{array}$$

Compd. No.	R ₂ N	R'X	M.p., °C.	Formula	Analyses, %			
					Carbon		Hydrogen	
				Calcd.	Found	Calcd.	Found	
(A) $n = 2$								
1	Dimethylamino	CH ₃ Cl	270-271	C ₁₂ H ₂₈ Cl ₂ N ₄ O ₂	43.5	43.5	8.5	8.5
2	Diethylamino		85-86	C ₁₄ H ₃₀ N ₄ O ₂	58.7	58.4	10.5	10.1
3	Diethylamino	CH ₃ I	210-211	C ₁₆ H ₃₄ I ₂ N ₄ O ₂	33.7	34.1	6.4	6.7
4	Pyrrolidino		115-116	C ₁₄ H ₂₆ N ₄ O ₂	59.6	59.2	9.3	9.1
5	Pyrrolidino	CH ₃ I	227-228	C ₁₆ H ₃₂ I ₂ N ₄ O ₂	34.0	33.8	5.7	5.5
6	Piperidino		138-139	C ₁₆ H ₃₀ N ₄ O ₂	61.9	61.9	9.8	10.0
7	Morpholino		191-192	C ₁₄ H ₂₆ N ₄ O ₄	53.4	53.5	8.3	8.1
(B) $n = 3$								
8	Dimethylamino	CH ₃ Cl	238-239	C ₁₈ H ₃₀ Cl ₂ N ₄ O ₂	45.2	45.4	8.8	8.9
9	Diethylamino	HCl	155-156	C ₁₆ H ₃₄ Cl ₂ N ₄ O ₂	48.2	48.2	9.2	9.3
10	Diethylamino	CH ₃ I	151-152	C ₁₇ H ₃₂ I ₂ N ₄ O ₂	34.9	35.1	6.6	6.8
11	Piperidino		83-84	C ₁₇ H ₃₂ N ₄ O ₂	63.0	63.1	9.9	9.8
12	Piperidino	CH ₃ I	203-204	C ₁₉ H ₃₈ I ₂ N ₄ O ₂	37.5	37.5	6.3	6.1
13	Morpholino		153-154	C ₁₅ H ₂₈ N ₄ O ₄	54.9	54.6	8.6	8.3
14	Morpholino	CH ₃ I	182-183	C ₁₇ H ₃₄ I ₂ N ₄ O ₄	33.3	33.1	5.6	5.5
(C) $n = 6$								
15	Dimethylamino	CH ₃ Cl	232-233	C ₁₆ H ₃₆ Cl ₂ N ₄ O ₂	49.6	49.3	9.4	9.4
16	Diethylamino		61-62	C ₁₈ H ₃₈ N ₄ O ₂	63.1	62.9	11.2	11.1
17	Diethylamino	CH ₃ I	116-118	C ₂₀ H ₄₄ I ₂ N ₄ O ₂	38.4	38.8	7.1	7.2
18	Pyrrolidino		82-83	C ₁₈ H ₃₄ N ₄ O ₂	63.9	63.9	10.1	10.0
19	Pyrrolidino	CH ₃ I	137-138	C ₂₀ H ₄₀ I ₂ N ₄ O ₂	38.6	38.6	6.5	6.7
20	Piperidino		108-109	C ₂₀ H ₃₈ N ₄ O ₂	65.6	65.8	10.4	10.1
21	Piperidino	CH ₃ I	175-176	C ₂₂ H ₄₄ I ₂ N ₄ O ₂	40.6	40.3	6.8	6.7
22	Morpholino		85-86	C ₁₈ H ₃₄ N ₄ O ₄	58.4	58.5	9.3	8.9
23	Morpholino	CH ₃ I	175-176	C ₂₀ H ₄₀ I ₂ N ₄ O ₄	36.7	36.4	6.2	6.1
(D) -NH(CH ₂) _n NH-replaced by piperazino-1,4-								
24	Dimethylamino	CH ₃ Cl	290 (dec.) sinters from 245°	C ₁₄ H ₃₀ Cl ₂ N ₄ O ₂ ·H ₂ O	44.8	44.7	8.6	8.3
(E) -NH(CH ₂) _n NH-replaced by NH-  -NH								
25	Dimethylamino	CH ₃ Cl	296-298 (dec.)	C ₁₆ H ₂₈ Cl ₂ N ₄ O ₂	50.6	50.6	7.4	7.2

ries.^{7,8} Compounds 6 and 20 of Table I ($n = 2$ and $n = 6$, respectively) were equally active and both were among the most potent of the group described here.

Variations in the end-group structure were more critical for activity, and the results obtained with the present series paralleled the findings with the older amides^{7,8} in this regard. Thus the morpholino derivatives were inactive. The methiodides of simple dialkylamino derivatives were somewhat more active than the ditertiary amines. The most potent compounds had piperidino or pyrrolidino as end-groups, and for these types the bis-tertiary-aminoamides were from 5-20 times more active than the derived bis-methiodides as prolongers of succinylcholine.

Other useful activities have been observed with these amides. They resemble Prostigmine and Tensilon in their ability to antagonize *d*-tubocurarine chloride. Various members act as respiratory stimulants.

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Experimental

N,N'-Bis-chloroacetylhexamethylenediamine.—To a solution of 23 g. (0.2 mole) of chloroacetyl chloride in 500 cc. of absolute ether was added gradually with cooling and stirring 23 g. (0.2 mole) of hexamethylenediamine (as 70% aqueous solution). The addition took 0.5-1 hour and stirring was continued for 2 hours longer. A white pasty precipitate formed during the addition of the amine. After 2 hours the pasty solid was filtered off by suction and washed several times with small volumes of ether. The total crude yield of bis-amide and diamine dihydrochloride was 58 g. (100%). The crude mixture was heated with 100 cc. of water and on cooling gave 20 g. (70-75%) of bis-chloroacetylamine. After two additional recrystallizations from hot ethyl acetate the yield was 12-15 g. (50-55%) of amide melting at 131-132°.

Anal. Calcd. for C₁₀H₁₈Cl₂N₂O₂: C, 44.7; H, 6.7. Found: C, 44.9; H, 6.8.

The other bis-chloroacetylaminides were made by similar procedures. Yields of pure products were usually 35-50%. Melting points corresponded with those reported in the literature.¹⁰⁻¹³

Preparation of the Bis-aminoacetylaminides.—A mixture of 0.01 mole of the bis-chloroacetylamine and 0.06-0.1 mole of the amine, either in methanol solution or without solvent,

was heated for 2–4 hours at 100°. Any excess of unused amine and solvent was removed by evaporation *in vacuo*. The residue was basified with a small amount of cold 20% aqueous sodium hydroxide (to pH 11) and the precipitated solid bis-aminoamide was collected by suction and washed with a little cold water. The products were purified by recrystallization from ethyl acetate, hexane or mixtures of these solvents. Yields were usually above 90%.

The bis-tertiary-aminoacetyl amides were quaternized by refluxing with methyl iodide in methanol for several hours. The bis-methiodides crystallized from methanol or methanol–ethyl acetate mixtures. Yields were all above 90%.

Details for all compounds appear in Table I.

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Antifungal Agents¹

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A series of tertiary aliphatic and heterocyclic amines have been prepared and examined as antifungal agents for pathogenic molds and fungi. Certain structure–activity relationships are evident and are discussed.

With the advent of broad-spectrum antibiotics which somewhat indiscriminately destroy both malevolent and benevolent bacteria within the human host, the development of pathogenic fungal infections has received considerable attention.² Although there is apparently no completely satisfactory method for combatting fungal infections arising from *M. albicans* and *T. mentagrophytes*, whose overgrowth may be made possible by the destruction of competitive flora, the true incidence of the condition, specifically moniliasis, is still questionable.² Despite considerable work and the evolution of several theories, the mechanism whereby *M. albicans* acquires pathogenesis following antibiotic therapy is still obscure.

Despite the lack of agreement among clinicians regarding the need for antifungal agents specifically effective against pathogenic fungi, various types of fungicides are in clinical use or under investigation. Being cognizant of the anti-monilial properties of a group of steroidal amines and their quaternary salts³ as well as the fungistatic and fungicidal action of certain long chain saturated and unsaturated fatty acids,⁴ it was of interest to prepare and examine microbiologically a series of saturated and unsaturated tertiary amines and salts thereof.

The compounds prepared in this study are of the general formula $R_1NR_2R_3$ wherein R_1 is a saturated or unsaturated hydrocarbon group and $-NR_2R_3$ is a dialkylamino, pyrrolidino, piperidino and morpholino group. It is to be noted that these compounds combine the hydrocarbon moiety of the fatty acids⁴ and the basic moiety of the steroidal amines.³

The tertiary amines were prepared by conventional methods, the procedure of choice being the reaction of the appropriate acid chloride and

secondary amine to the intermediate amide (see Table I) followed by reduction of the amide with lithium aluminum hydride.⁵

The amides, tertiary amines and the acid addition and quaternary salts of the latter were submitted to an *in vitro* microbiological test to determine their activity against *Monilia albicans*, *T. mentagrophytes* (Table II) as well as *E. coli*, *P. aeruginosa*, *S. aureus*, *B. subtilis* and *M. smegmalis*. The antifungal activities of the compounds were compared with two fungicides in clinical use, undecylenic acid and 6-(β -diethylaminoethoxy)-2-dimethylaminobenzothiazole dihydrochloride.⁶ In order to obtain sufficient data for a structure correlation several known tertiary amines were prepared and examined.

All the compounds were essentially inactive against *E. coli* and *P. aeruginosa*. The amides exhibited activities which were neither of sufficient magnitude nor broadness of spectrum as to warrant reporting. From Table II certain relationships between structure and activity are manifest. It is of interest to note that within the confines of the optimum structures all compounds possessed antifungal activities greater than that of undecylenic acid and in most cases in excess of that possessed by Asterol.

Optimum activity resides in those compounds wherein $R_1 = 10$ -undecenyl, and R_2 and R_3 contain a total of 4–6 carbon atoms (X, XIII, XIV, XV and XVI). Increasing the carbon chain in R_2 and R_3 to isobutyl (XI) or shortening to methyl (IX) markedly reduced activity.

Hydrogenation of the terminal double bond of compound X did not radically alter the antifungal activity (XIX) whereas transforming the ethylenic bond to an acetylenic link narrows the spectrum (XII). The pronounced activity of XIX was of interest since this investigation was originally based upon the supposition that the terminal unsaturation was a prerequisite for activity. Wyss, *et al.*,⁴ demonstrated the rather singular properties of undecylenic acid as a fungicide.

Having somewhat empirically shown the effect

(1) Presented in abstract at The North Jersey Miniature Meeting in Newark, New Jersey, January 24, 1955.

(2) (a) M. J. Lipnik, A. M. Kligman and R. Strauss, *J. Investigative Dermat.*, **18**, 247 (1952); (b) W. I. Metzger, L. T. Wright and J. C. DiLorenzo, *J. Am. Med. Assoc.*, **155**, 352 (1954).

(3) (a) F. C. Kull, G. A. Castellano and R. L. Mayer, *J. Investigative Dermat.*, **21**, 227 (1953); (b) Hershel L. Herzog, Constance C. Payne and E. B. Hershberg, to be published.

(4) (a) O. Wyss, B. J. Ludwig and R. R. Joiner, *Arch. Biochem.*, **7**, 415 (1945); (b) J. Kimmig and H. Rieth, *Arzneim. Forsch.*, **3**, 267 (1953).

(5) The reduction (and isolation) was essentially that described by V. Micovic and M. Mihailovic, *J. Org. Chem.*, **18**, 1190 (1953).

(6) Asterol—Registered trade mark of Hoffmann-LaRoche, Inc.