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Potential Antiviral Agents. II. Analogs of Tetraalkyldiamines

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RECEIVED SEPTEMBER 26, 1955

A series of diamine analogs of the general formula $R^1R^2NCH_2CH_2R^3$ was prepared for evaluation as antiviral, antifungal, antibacterial and local anesthetic agents. None of the compounds prepared was found to possess therapeutically useful properties.

The discovery in these laboratories that dialkylaminoethylenediamines of the general formula I, wherein the sum of R^1 and R^2 may be 8 to 13, possess a significant degree of antiviral activity[1] was regarded as a valuable "lead" for the synthesis of compounds of even greater antiviral activity and potential therapeutic application. It was thought of some importance, therefore, to determine the limits of structural variation of compounds of type I which are possible without loss of antiviral activity.

$$R^1R^2NCH_2CH_2N(CH_3)_2$$
I

Ia, $R^1 = n\text{-}C_9H_{19}$, $R^2 = CH_3$
b, $R^1 = n\text{-}C_7H_{15}$, $R^2 = C_3H_7$

In a previous communication[2] the synthesis and properties were described of a variant of 1b wherein *n*-heptyl was replaced by 2-nitroisobutyl. In this paper, the results are reported of a study of additional variants (Table I) of type I which may be regarded as having been obtained from Ia and Ib by replacement of the dimethylamino group by carboxy, carboxamido, thiocyano and cyclic basic groups.

(A) $R^1R^2NH + Cl(CH_2)_2N\langle\rangle S \longrightarrow R^1R^2N(CH_2)_2N\langle\rangle S$

(B) $R^1R^2N(CH_2)_2Cl + HN\langle\rangle \longrightarrow R^1R^2NCH_2CH_2N\langle\rangle$

(C) $R^1R^2NCH_2CN + Na + HOC_4H_9 \longrightarrow R^1R^2NCH_2CH_2NH_2$

(D) $R^1R^2NCH_2CN + H_2SO_4 \longrightarrow R^1R^2NCH_2CONH_2$

The glycinenitriles which were required for the preparation of the primary amines (reaction C) and carboxamides (reaction D) described in Table I appeared to be satisfactory starting materials for the synthesis of imidazolines. All attempts, however, to convert these nitriles to imidazolines (compounds 5 and 6, Table I) by the action of hydrogen sulfide and ethylenediamine at 100° under pressure[3] or stepwise by conversion of the nitriles to thioamides[4] or imidic esters followed by cyclization with ethylenediamine resulted only in the recovery of unreacted starting materials. The desired imidazolines were eventually prepared with no difficulty by in-

TABLE I

DIAMINE ANALOGS, $R^1R^2N(CH_2)_nR^3$

No.	R^1	R^2	R^3	Method of prepn.[a]	n	B.p., °C.	Mm.	$n^{25}D$	Empirical formula	Nitrogen, % Calcd.	Found
1	$n\text{-}C_7H_{15}$	$i\text{-}C_3H_7$	NH_2	C	2	81–82	0.3	1.4427	$C_{12}H_{28}N_2$[b,c]	..	..
2	$n\text{-}C_9H_{19}$	CH_3	NH_2	C	2	95–97	1.0	1.4461	$C_{12}H_{28}N_2$[b,d]	..	..
3	$n\text{-}C_7H_{15}$	$i\text{-}C_3H_7$	$1\text{-}C_4H_8N$	B	2	78–80	0.1	1.4570	$C_{16}H_{34}N_2$	11.0	10.9
4	$n\text{-}C_9H_{19}$	CH_3	$1\text{-}C_4H_8N$	B	2	87–89	.1	1.4578	$C_{16}H_{34}N_2$	11.0	10.7
5	$n\text{-}C_7H_{15}$	$i\text{-}C_3H_7$	$2\text{-}C_3H_5N_2$	A	1	115–116	.2	[e]	$C_{14}H_{29}N_3$	17.6	17.7
6	$n\text{-}C_9H_{19}$	CH_3	$2\text{-}C_3H_5N_2$	A	1	103–104	.05	[e]	$C_{14}H_{29}N_3$	17.6	17.2
7	$n\text{-}C_7H_{15}$	$i\text{-}C_3H_7$	$1\text{-}C_5H_{10}N$	B	2	110–116	1	1.4612	$C_{17}H_{36}N_2$	10.4	10.0
8	$n\text{-}C_7H_{15}$	$i\text{-}C_3H_7$	$1\text{-}C_4H_8NO$	A	2	128–132	1	1.4595	$C_{16}H_{34}N_2O$	10.4	10.6
9	$n\text{-}C_9H_{19}$	CH_3	$1\text{-}C_4H_8NO$	A	2	122–124	0.3	1.4593	$C_{16}H_{34}N_2O$	10.4	10.3
10	$n\text{-}C_7H_{15}$	$i\text{-}C_3H_7$	$4\text{-}C_4H_8NS$	A	2	126–127	.3	1.4850	$C_{16}H_{34}N_2S$	9.8	9.6
11	$n\text{-}C_7H_{15}$	$i\text{-}C_3H_7$	$4\text{-}C_{11}H_{15}N_2$	B	2	170–171	.3	1.5020	$C_{23}H_{41}N_3$	11.7	11.6
12	$n\text{-}C_9H_{19}$	CH_3	$4\text{-}C_{11}H_{15}N_2$	B	2	158–158.5	.1	1.5018	$C_{23}H_{41}N_3$	11.7	11.5
13	$n\text{-}C_7H_{15}$	$i\text{-}C_3H_7$	$CONH_2\cdot HCl$	D	1	[f]		....	$C_{12}H_{27}N_2OCl$	11.2	11.1
14	$n\text{-}C_9H_{19}$	CH_3	$CONH_2\cdot HCl$	D	1	[g]		....	$C_{12}H_{27}N_2OCl$	11.2	11.1
15	$n\text{-}C_{12}H_{25}$	CH_3	COONa	A	1	[h]		....	$C_{15}H_{30}NO_2Na$	5.02	4.99
16	$n\text{-}C_7H_{15}$	$i\text{-}C_3H_7$	SCN	B	2	131–135	0.7	1.4778	$C_{13}H_{26}N_2S$	11.6	11.2

[a] For details see Experimental section. [b] Carbon–hydrogen determination by Schwarzkopf Microanalytical Labs., Woodside, N. Y. [c] Calcd.: C, 71.93; H, 14.06. Found: C, 72.19; H, 13.91. [d] Calcd.: C, 71.93; H, 14.06. Found: C, 72.14; H, 14.00. [e] Crystallized on standing to a low melting solid. [f] M.p. 123–124°; recrystallized from a mixture of ethanol and ether. [g] M.p. 127–128°; recrystallized from a mixture of ethanol and ether. [h] M.p. 185–190°; recrystallized from ethanol.

The compounds in Table I were prepared by conventional procedures which are illustrated by examples A to D

(1) Unpublished data collected in these laboratories.

(2) F. Leonard and F. E. Anderson, THIS JOURNAL, **77**, 4425 (1955).

(3) H. Isler, U. S. Patent 2,505,247 [*C. A.*, **44**, 6888 (1950)].

(4) This was attempted both by treating alcoholic solutions of the nitriles with gaseous ammonia and hydrogen sulfide at 100° and pressure and utilizing the pyridine–triethylamine–hydrogen sulfide procedure of A. E. S. Fairfull, J. L. Lowe and D. A. Peak, *J. Chem. Soc.*, 742 (1952).

teraction of 2-chloromethylimidazoline with the requisite secondary amines.

The compounds described in Table I as bases were converted to hydrochlorides for testing by dissolution in water containing an equivalent of hydrochloric acid and evaluated for antiviral, antibacterial and antifungal activity. None of the compounds was found to possess a higher order of antiviral activity than Ia or Ib. Several (2, 7, 8, 12, 16) of the compounds showed activity comparable to that which was demonstrated by the moderately active parent diamines[5]; one (16) possessed a broad spectrum of antifungal activity comparable to that of aspergillic acid.[6] None of the compounds showed useful local anesthetic properties.

Acknowledgment.—Evaluation of the microbiological and local anesthetic properties of our compounds was carried out, respectively, under the direction of Drs. F. A. Barkley and R. J. Schachter in these laboratories. Miss R. Becker supplied the analytical data and Miss A. Stern assisted in the preparation of several intermediates.

Experimental

Basic-alcohols.—Addition at 50° of ethylenebromohydrin dissolved in an equal volume of benzene to a 100% excess of the requisite amine in four volumes of benzene followed by a reflux period of 17 hours gave on workup in the usual way the new basic-alcohols in Table II. Treatment of morpholine in excess with ethylene bromohydrin yielded 2-(4′-morpholinyl)-ethanol.[7] The action of gaseous hydrogen bromide on di-(2-hydroxyethyl) sulfide gave di-(2-bromoethyl) sulfide[8] which on interaction with ethanolamine in excess[8] yielded 2-(4-thiamorpholinyl)-ethanol hydrochloride.

TABLE II

$R^1R^2NCH_2CH_2OH$

R^1	R^2	Yield, %	B.p., °C.	Mm.	$n^{25}D$	Nitrogen, % Found[a]
n-C_7H_{15}	i-C_3H_7	50	129–130	10	1.4442	7.07
n-C_9H_{19}	CH_3	46	94–100	1	1.4486	7.24

[a] Calcd. for $C_{12}H_{27}NO$: N, 6.99.

Basic-alkyl Chlorides.—The basic alcohols described above were dissolved in four volumes of dry benzene and treated with cooling (35°) and stirring with a 100% excess of thionyl chloride dissolved in one volume of benzene and then refluxed. The known basic-alkyl chlorides gave crystalline hydrochlorides which were filtered, washed with benzene and dried. The new compounds gave sirupy hydrochlorides which were accordingly isolated as the free bases by treatment of the sirupy residues obtained on concentration of the reaction mixtures with 40% sodium hydroxide and extraction with ether. Data on these compounds are given in Table III.

2-Chloromethylimidazoline was prepared by stepwise conversion of chloroacetonitrile to ethyl chloroacetimidate hydrochloride following the directions of Schmidt[9] and treatment of the imidic ester with ethylenediamine according to Klarer and Urech.[10]

N,N-Dialkylglycinenitriles.—Cyanomethylation of n-heptylisopropylamine and methyl-n-nonylamine was accomplished using the procedure developed by Turner and Djerassi[11] for the preparation of N-benzyl-N-phenylglycinenitrile.

N-(n-Heptyl)-N-(isopropyl)-glycinenitrile was obtained in 80% yield as a pale yellow oil which distilled at 93–96° (0.8 mm.), $n^{25}D$ 1.4405. *Anal.* Calcd. for $C_{12}H_{24}N_2$: N, 14.3. Found: N, 14.0.

N-Methyl-N-(n-nonyl)-glycinenitrile was prepared in the same way in 80% yield, b.p. 105–110° (1.3 mm.), $n^{25}D$ 1.4392. *Anal.* Calcd. for $C_{12}H_{24}N_2$: N, 14.3. Found: N, 14.2.

The following examples illustrate the procedures employed in the preparation of the compounds in Table I.

Method A. Sodium N-(n-Dodecyl)-N-methylglycinate.—Bromoacetic acid (8.7 g., 0.0625 mole) was added with stirring in small portions to 49.9 g. (0.25 mole) of n-dodecylmethylamine. The temperature of the reaction mixture rose to 45°. The mixture was stirred for 1.5 hours without heating, then at 65° for five hours, diluted with 50 ml. of water and made basic with 30 ml. of 10 N sodium hydroxide. Addition of ether to extract excess n-dodecylmethylamine gave a homogeneous mixture which was not disturbed by addition of water. The solution was thereupon extracted with petroleum ether and the aqueous layer evaporated *in vacuo* (severe foaming). The solid residue was dissolved in alcohol, filtered and precipitated by addition of five volumes of acetone. Recrystallization from ethanol gave analytically pure sodium N-(n-dodecyl)-N-methylglycinate.

Method B. 1-Benzyl-4-[2-(methyl-n-nonylamino)-ethyl]-piperazine.—A mixture of 5.5 g. (0.025 mole) of 2-(methyl-n-nonylamino)-ethyl chloride (8.8 g., 0.05 mole) of 1-benzylpiperazine[12] and 50 ml. of dry benzene was refluxed overnight. The cooled reaction mixture was filtered to remove 1-benzylpiperazine hydrochloride, the filter cake washed with benzene and the filtrate fractionated. The 1,4-disubstituted piperazine distilled at 164–166° (0.1 mm.), $n^{25}D$ 1.5018, yield 7.5 g. (95%). A sample refractionated for analysis distilled at 158–158.5° (0.1 mm.) but showed no change in refractive index.

Method C. N-(n-Heptyl)-N-isopropylethylenediamine.—The specific conditions of the sodium–butanol reduction of N,N-dialkylglycinenitriles described by Bloom, *et al.*,[13] were modified for the reduction of our nitriles. Sodium (0.6 g.-atom) was converted to sodium sand in 75 ml. of dry toluene and with good stirring treated dropwise with a solution of 19.6 g. (0.1 mole) of N-(n-heptyl)-N-(isopropyl)-glycinenitrile in 50 ml. of dry n-butyl alcohol while maintaining the temperature of the reaction mixture at 100°. After completion of addition of the nitrile (*ca.* 0.5 hour) the mixture was stirred and refluxed for one hour and let cool. The gelatinous mass, containing unreacted sodium, was broken by the addition of methanol and the result-solution poured into an ice–water mixture. The mixture thereafter was worked up as described by Bloom, *et al.*

TABLE III

BASIC ALKYL CHLORIDES

	Hours refluxed	Yield, %	Physical data
2-(4-Morpholinyl)-ethyl, hydrochloride[a]	4	95	M.p., 178–180
2-(4-Thiamorpholinyl)-ethyl, hydrochloride[b]	4	74	M.p., 204–205
2-(n-Heptylisopropyl-amino)-ethyl[c]	5	78	B.p., 90–93 (2 mm.) $n^{25}D$ 1.4466
2-(Methyl-n-nonyl-amino)-ethyl[d]	15	20	B.p., 96–104 (1 mm.)

[a] J. P. Mason and H. W. Block, THIS JOURNAL, **62**, 1445 (1940), reported m.p. 182–182.5. [b] H. Gilman and L. A. Woods, *ibid.*, **67**, 1843 (1946), claimed the preparation of this compound in 95% yield, and m.p. 206–208° using chloroform for the reaction solvent but gave no experimental details. We found benzene to be more satisfactory a solvent for this reaction. [c] *Anal.* Calcd. for $C_{12}H_{26}ClN$: N, 6.36. Found: N, 6.79. [d] *Anal.* Calcd. for $C_{12}H_{26}ClN$: neut. equiv., 219.5. Found: neut. equiv., 216.

(5) G. F. Grail, L. E. Tenenbaum, A. V. Tolstoouhov, C. J. Duca, J. F. Reinhard, F. E. Anderson and J. V. Scudi, THIS JOURNAL, **74**, 1313 (1952).

(6) A tabulation of minimal effective concentration data and a description of the microbiological techniques employed for the evaluation of the compounds described herein will be submitted for publication elsewhere.

(7) F. Leonard and L. Simet, THIS JOURNAL, **77**, 2855 (1955).

(8) L. A. Burrows and E. E. Reid, *ibid.*, **56**, 1720 (1934).

(9) E. Schmidt, *Ber.*, **47**, 2547 (1914).

(10) W. Klarer and E. Urech, *Helv. Chim. Acta*, **27**, 1773 (1944).

(11) R. A. Turner and C. Djerassi, THIS JOURNAL, **72**, 3081 (1950).

(12) R. Baltzly, J. S. Buck, E. Lorz and W. Schon, *ibid.*, **66**, 264 (1944).

(13) M. S. Bloom, D. S. Breslow and C. R. Hauser, *ibid.*, **67**, 539 (1946).

Method D. N-Methyl-N-(*n*-nonyl)-glycineamide Hydrochloride.—N-Methyl-N-(*n*-nonyl)-glycinenitrile (4.4 g.) was added dropwise with shaking to 9 ml. of concentrated sulfuric acid at −10°, the mixture stored at room temperature for 72 hours and subsequently poured into cracked ice. The resulting mixture was basified, extracted with ether, and the extract dried over anhydrous potassium carbonate. Potassium carbonate was separated and the benzene solution evaporated to dryness. The residue, a waxy, white solid, melted at 59–62°, crude, and at 63–63.5° after two recrystallizations from an alcohol–water mixture; yield 3.5 g. after recrystallization. A portion (1.7 g.) of the amide, dissolved in ethanol was converted to the amide hydrochloride in a quantitative yield.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

Derivatives of Sulfenic Acids. XXIII. The Effects of *para*-Substituents in Styrene on the Kinetics and Mechanism of the Reaction with 2,4-Dinitrobenzenesulfenyl Chloride[1]

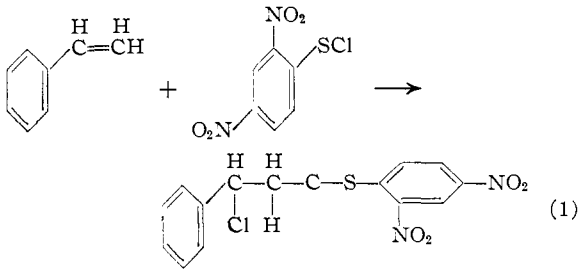
BY WILSON L. ORR AND NORMAN KHARASCH

RECEIVED JULY 5, 1955

The effects of the *para*-substituents, Cl, $-CH_3$ and $-NO_2$, in styrene, on the measured second-order rate constants for the reaction of 2,4-dinitrobenzenesulfenyl chloride with the respective olefins, in dry acetic acid, fit the Hammett equation excellently, with *rho* being −2.20 at 25°. The differences in rates are determined mainly by differences in the activation energies, but significant variations in the entropies of activation occur. The reaction with *p*-methoxystyrene was too fast for rate measurements at 25°, was complicated by polymerization, and the vinyl sulfide $CH_3O—C_6H_4—CH=CH—SAr$ (Ar = 2,4-dinitrophenyl), rather than the 1:1 adduct was formed. At 10–13°, however, up to 86% of the 1:1 adduct, together with the vinyl sulfide and 3–6% of the β-acetoxy sulfide was formed. The 1:1 adduct is not the intermediate whereby the vinyl sulfide forms, at 25°, as shown by studies of the rate of dehydrohalogenation of the adduct into the vinyl sulfide at this temperature. The vinyl sulfide probably arises directly by loss of proton from the intermediate sulfonium ion.

Introduction

A previous paper[2] reported a detailed study of the kinetics and mechanism of the reaction of 2,4-dinitrobenzenesulfenyl chloride (I) with styrene (eq. 1)



(1)

The purpose of the present work was to evaluate the effects of *para*-substituents, in the styrene, on the reactions corresponding to equation 1. Such a study was desirable, since it could clearly demonstrate the relation of electron density, *i.e.*, nucleophilic character, of the carbon–carbon double bond on the rate and course of the olefin–sulfenyl halide reaction and would also test whether the well-known[3,4] Hammett rho–sigma equation applies to this reaction. A negative reaction constant, rho, was anticipated on the basis of a previous proposal[2] for the reaction mechanism, which suggested electrophilic attack by I on the olefin bond, *via* a cyclic sulfonium ion, as the rate-determining step.

When this work was begun, the Hammett equation had not been applied to an "ionic addition reaction" at the olefinic bond.[5] In the interim, however, Overberger and co-workers[6] have reported on the stannic chloride-catalyzed copolymerization of styrene and *para*-substituted styrenes, and correlated their rate data by the Hammett equation. As noted below, their results relate interestingly to the present study.

Kinetic Data.—*p*-Nitro-, *p*-chloro-, *p*-methyl- and *p*-methoxystyrene were selected for study. Rates were measured as described previously,[2] using dry acetic acid as solvent to allow comparisons with the earlier rate data for styrene itself. The rates with *p*-nitro-, *p*-chloro- and *p*-methylstyrenes were measured, and satisfactory second-order rate constants were established for these reactions. All the determinations were carried to 80–90% completion and the products were the 1:1 adducts of I and the particular styrene, in each case. As discussed below, however, the reaction of I with *p*-methoxystyrene was complicated, and only an approximate estimate of the rate constant, at 25°, could be made in this case.

The second-order rate constants and the Arrhenius parameters, A and E_a, are given in Table I. Except for the single run at 44.9° for the *p*-methyl homolog, which showed a positive curvature, and the data for *p*-methoxystyrene (*cf.* experimental) all the runs gave excellent, second-order plots, comparable to those obtained earlier[2] for styrene. The complete data for individual runs are not reported here, but are available.[7] The entropies of activation, $\Delta S^{\ddagger}$, calculated from the frequency factors, A, are also tabulated.

The data of Table I show that the rates of addition of the sulfenyl chloride are favored by elec-

(1) This study was sponsored by the Office of Ordnance Research, United States Army, Contract DA-04-495-Ord. 306.

(2) W. L. Orr and N. Kharasch, THIS JOURNAL, **75**, 6030 (1953).

(3) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 186–194.

(4) H. H. Jaffe, *Chem. Revs.*, **53**, 191 (1953).

(5) The previous non-existence of such studies may be attributed to the fact that many "ionic addition reactions" with suitable olefins are too fast to measure conveniently, and because the reactions are often complicated by side reactions (*e.g.*, substitutions or polymerizations) or they do not clearly involve a single reaction mechanism.

(6) C. G. Overberger, L. H. Arnold, D. Tanner, J. J. Taylor and T. Alfrey, THIS JOURNAL, **74**, 4848 (1952).

(7) W. L. Orr, Doctoral Dissertation, University of Southern California, June, 1954; available in microfilm copy.