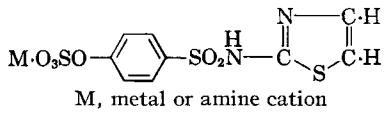
Mannich Bases of Phenolsulfonamides: Derivatives of N-(2-Thiazolyl)-1-phenol-4-sulfonamide

By GEORGE M. SIEGER, WILLIAM C. BARRINGER, FRANCIS M. CALLAHAN, NORBERT GRUENFELD, and JOSEPH F. WEIDENHEIMER

A series of Mannich base derivatives of N-(2-thiazolyl)-1-phenol-4-sulfonamide has been synthesized and characterized largely in the form of hydrochloride salts and acetyl derivatives. The results on a variety of biological screening tests carried out on these compounds have been reported.

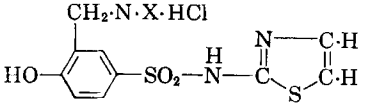
SOME TIME ago an interest was expressed by these laboratories in a series of phenolsulfonamides, namely, N-(2-thiazolyl)-1-phenol-4-sulfonamides[1] and analogs as a potential chemotherapeutic agent for certain neurotropic virus diseases (1–3, 7). More complete and exhaustive testing of these compounds gave indication that these compounds were not as effective against certain viruses as initially thought (8). However, before these biological results were reported, it was decided that water-soluble derivatives of the phenolsulfonamides should be prepared as a possible means of improving their pharmaceutical utility. One means of effecting water solubility was to prepare phenolic hemi-sulfuric esters of the phenolsulfonamides that could be isolated as metal and/or amine salts; this work was carried out by Hultquist and Webb (2). These compounds can be represented by general formula A.



M, metal or amine cation

A

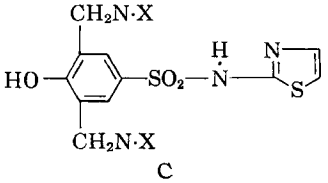
In these laboratories another approach to the problem was initiated at the time and some work has been pursued intermittently in this area over a period of years. It involved the synthesis of Mannich base derivatives which could be prepared and isolated as water-soluble acid salts, where ·N·X in the studies was represented by substituted secondary heterocyclic and dialkyl



B

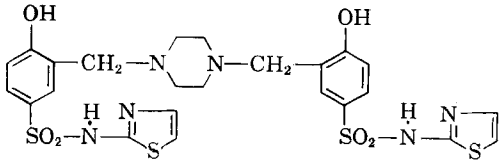
amines, e. g., morpholine, piperidine, pyrrolidine, piperazines, diethylamine, and dimethylamine.

The phenolsulfonamides, having both *ortho* positions to the phenolic hydroxyl group free and the *meta* directing sulfonamido group in the position *para* to the hydroxyl, have lent themselves readily to Mannich condensations. Other general types of compounds that theoretically could be derived from the Mannich condensations on N-(2-thiazolyl)-1-phenol-4-sulfonamide are: a di-Mannich base substituted into both positions *ortho* to the phenolic hydroxyl, i. e.,



C

and a Mannich base in which two phenolsulfonamide molecules are joined to both amine nitrogens of a di-functional amine, such as piperazine, by means of a methylene bridge, e. g.,



D

In order to identify and characterize these compounds, the Mannich bases were isolated as free bases, hydrochloride salts, and/or acetyl derivatives. In Table I are listed the compounds prepared, their respective identifying numbers, their names, melting points, yield, and micro-

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[1] N-(2-Thiazolyl)-1-phenol-4-sulfonamide is also known and tested under the names phenosulfazole and Darvisul.

TABLE I.—CHARACTERIZATION OF COMPOUNDS PREPARED

No.	Compound	Empirical Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Chlorine Calcd.	Chlorine Found	Nitrogen Calcd.	Nitrogen Found	Sulfur Calcd.	Sulfur Found	Approx. Yield, %	M. P. (with Decompn.) °C.	Crystallization Solvents
I	2-(4-Morpholinomethyl)-N-(2-thiazolyl)-1-phenol-4-sulfonamide	$C_{14}H_{17}N_3O_4S_2$	47.31	47.17	4.82	5.01	...	...	11.82	11.41	18.04	18.0	71.7	194–197	DMF[b]-H_2O
Ia	Hydrochloride	$C_{14}H_{18}ClN_3O_4S_2$	42.90	42.86	4.63	4.96	9.05	9.23	10.72	10.82	16.36	16.58	62.0	195–198	H_2O
Ib	Acetyl derivative	$C_{16}H_{19}N_3O_5S_2$	48.35	48.82	4.82	5.19	...	...	10.57	10.37	16.13	15.95	25.0	165–167	Acetone-H_2O
II	2-(Piperidinomethyl)-N-(2-thiazolyl)-1-phenol-4-sulfonamide	$C_{15}H_{19}N_3O_3S_2$	50.97	50.40	5.42	5.73	...	...	11.89	11.83	...	...	70.6	202–203	DMS[c]-EtOH
IIa	Hydrochloride	$C_{15}H_{20}ClN_3O_3S_2$	46.20	46.23	5.17	5.38	9.09	8.83	10.78	10.59	16.45	16.23	50.0	185–189	MeOH-EtOH-Ether
IIb	2,6-Bis compound dihydrochloride	$C_{21}H_{32}Cl_2N_4O_3S_2$	48.17	48.33	...	...	13.54	13.68	10.70	10.72	...	...	8.0	184–191	DMF-50-50 Iso-PrOH-Pet. Ether
III	2-(Pyrrolidylmethyl)-N-(2-thiazolyl)-1-phenol-4-sulfonamide	$C_{14}H_{17}N_3O_3S_2$	49.54	49.15	5.05	5.09	...	...	...	...	18.89	18.50	73.7	193–196	DMS-EtOH
IIIa	Hydrochloride	$C_{14}H_{18}ClN_3O_3S_2$	44.73	45.00	4.83	4.88	9.43	9.22	11.18	11.33	17.06	17.7	40.0	204–206	EtOH-Ether
IV	N,N'-Di-[N-(2-thiazolyl)-5-sulfonamido-2-hydroxybenzyl] piperazine	$C_{24}H_{26}N_6O_6S_4$	46.29	45.84	4.21	4.48	...	...	13.50	13.15	20.59	20.49	50.2	178–185	DMF-Acetone
IVa	Dihydrochloride	$C_{24}H_{28}Cl_2N_6O_6S_4$	41.43	41.39	...	...	...	..	...	...	...	...	95.6	220–250[a]	Iso-PrOH
V	2-(N-Methylpiperazinomethyl)-N-(2-thiazolyl)-1-phenol-4-sulfonamide	$C_{15}H_{20}N_4O_3S_2$	48.89	48.79	5.47	5.76	...	...	...	...	...	...	60.0	166–173	DMF-50-50 Iso-PrOH-Pet. Ether
Va	Dihydrochloride	$C_{15}H_{22}Cl_2N_4O_3S_2$	40.81	40.75	5.02	5.21	16.07	15.68	12.69	12.39	...	...	83.5	230–238[a]	Iso-PrOH-H_2O
VI	2-(Diethylaminomethyl)-N-(2-thiazolyl)-1-phenol-4-sulfonamide	$C_{14}H_{19}N_3O_3S_2$	49.24	48.64	5.61	5.50	...	...	...	...	18.78	18.96	56.8	205–208	Aqueous HCl-NaOH
VIa	Hydrochloride	$C_{14}H_{20}ClN_3O_3S_2$	44.49	44.29	5.33	5.35	9.38	9.24	11.12	11.22	16.97	17.12	57.7	161–163	Acetone-H_2O
VIb	Acetyl derivative	$C_{16}H_{21}N_3O_4S_2$	50.11	49.73	...	...	...	...	10.96	11.09	...	...	60.5	155–160	Acetone-H_2O
VII	2-(Dimethylaminomethyl)-N-(2-thiazolyl)-1-phenol-4-sulfonamide	$C_{12}H_{15}N_3O_3S_2$	45.99	46.09	4.82	5.00	...	...	13.41	13.50	20.46	20.05	83.8	202–205	MeOH
VIIa	Hydrochloride	$C_{12}H_{16}ClN_3O_3S_2$	41.19	41.08	4.61	4.83	10.14	10.08	12.01	11.90	18.33	18.38	91.5	209–220[a]	EtOH-H_2O

[a] Decomposed slowly over range indicated. [b] DMF, Dimethylformamide. [c] DMS, Dimethyl sulfoxide.

analytical data. By reference to Table I, it can be seen that compounds I, Ia, Ib, II, IIa, III, IIIa, V, Va, VI, VIa, VIb, VII, and VIIa would all have the basic type structure projected as general formula B.[2] Compound IIb is an example of general formula C and compounds IV and IVa represent examples of general formula D.[2]

Samples of representative types of compounds were submitted to the various testing groups to screen for any biological properties that they might possess. The types of activity tested for include: antibacterial and antifungal properties (*in vitro* and *in vivo*), general physiological properties, hypoglycemia, and activity against various parasite organisms and viruses. The results of these biological screening tests will be discussed under the Experimental part of this report.

EXPERIMENTAL DESIGN

The synthesis of the Mannich bases of N-(2-thiazolyl)-1-phenol-4-sulfonamide was carried out by condensing the phenolsulfonamide with the requisite molar proportions of formaldehyde solution and the desired secondary amine in a suitable solvent system (methanol was generally used) using slight modifications of the usual procedures for conducting Mannich reactions of phenols (4), which are described more completely under Experimental (*cf.* procedures A, B, and C). The proposed structures B, C, and D appear to be consistent with their infrared and ultraviolet spectra. For example, in compound types B and C, the infrared hydroxyl band is shifted to above 3 μ for the free Mannich base and is at the normal position of a free hydroxyl group in the hydrochlorides. This phenomenon might be explained by the occurrence of hydrogen bonding in this portion of the molecule.

When a hydrochloride is formed the free electrons on the nitrogen participate and are not free for bonding with the phenolic hydrogen, and the hydroxyl band returns to its normal position. If the Mannich substitution was at any position in the molecule other than *ortho* to the hydroxyl group the above phenomena would probably not occur.

The preparation of the hydrochloride salts (Ia, IIa, IIIa, IVa, Va, VIa, VIIa compounds) from the free bases of the Mannich base derivatives of the phenolsulfonamides was accomplished generally by treating the free base in a suitable solvent system (e. g., acetone, isopropanol, water, or aqueous acetone or isopropanol) with the requisite quantity of hydrogen chloride, either in the form of concentrated hydrochloric acid or hydrogen chloride gas. See procedure D of the Experimental for an example.

The synthesis of the acetyl derivatives (compounds Ib and VIb) of the phenolsulfonamide Mannich bases were effected by treating the compounds with the requisite quantity of acetic anhydride in the presence of pyridine in a suitable solvent system (acetone was used generally). The method used is a modification of many methods found in the literature, examples being the sulfonamide acetylation procedures used by Denton and Quinones (3) and Hoffer (5); see procedure E of the Experimental for a more complete description of the method.

Regarding the proposed structures for the mono-acetyl derivatives (Ib and VIb) of 2-(4-morpholinomethyl)-N-(2-thiazolyl)-1-phenol-4-sulfonamide (I) and 2-(diethylaminomethyl)-N-(2-thiazolyl)-1-phenol-4-sulfonamide (VI), some structural studies were carried out with the aid of infrared spectral analyses in an attempt to determine which of the two available sites for substitution, namely, the 1-phenol hydroxyl or the N^1-hydrogen, the mono-acetylation occurred. All evidence obtained in these studies gives strong evidence that the acetyl group is associated mainly with the 1-phenol position. The infrared curve of the mono-acetylated compounds (Ib and VIb) have C=O maxima at 5.70 μ and the ester peaks at 8.35 μ which is characteristic of phenolic or enolic acetyl ester derivatives. Furthermore, if the acetylation occurred at the N^1 position of the sulfonamide, there should be a maximum at 6.0 μ position of the curves but in all cases it is lacking.

EXPERIMENTAL

Synthesis of the Mannich Bases

Procedure A.—In general, the mono-Mannich bases of the phenolsulfonamides described by structural formula B were synthesized in a manner exemplified by the preparation of compound I.

2-(4-Morpholinomethyl)-N-(2-thiazolyl)-1-phenol-4-sulfonamide, I.—To 1 L. of methanol was added 256 Gm. (1 mole) of N-(2-thiazolyl)-1-phenol-4-sulfonamide and 95.7 Gm. (1.1 mole) of morpholine. On the mixing of these reagents, there was an exothermic reaction and a precipitation of a solid. Eighty-two milliliters (1.1 mole) of 37% formaldehyde solution was now added, the total mixture was stirred at room temperature until complete solution was attained. Finally a solid condensation product appeared. The mixture was heated on a water bath to about 50° for ten minutes. On cooling, more solid separated from the clear, orange liquid. The solid was filtered, suspended in 400 ml. of dimethylformamide, and the suspension was warmed on the steam bath until complete solution was obtained. To the solution was added 500 ml. of methanol and 1,000 ml. of water with stirring and the mixture was placed in the chillroom. Two more crops of product crystallized from the mother liquor and were collected. The crops were combined and dried in an oven at 56°; total yield, 254 Gm. (71.7%). The product melted (decompn.) 194 to 197°.

Anal.—Calcd. for $C_{14}H_{17}N_3O_4S_2$: C, 47.31; H, 4.82; N, 11.82; S, 18.04; mol. wt., 355.4. Found: C, 47.17; H, 5.01; N, 11.41; S, 18.0; mol. wt. by Menzies-Wright method, 350.

Procedure B.—This procedure illustrates the preparation of a di-Mannich base phenolsulfonamide described by structural formula C and exemplified by the preparation of compound IIb.

2,6 - Di - (piperidinomethyl) - N - (2 - thiazolyl)-

[2] The structures assigned to the Mannich bases reported in this paper, represented by general formulas B, C, and D, appear to be acceptable on the basis of microanalytical data, molecular weight determinations, ultraviolet and infrared studies, and an application of the classical rules of substitution and orientation.

1 - phenol - 4 - sulfonamide dihydrochloride, IIb.—Starting with 51.4 Gm. (0.2 mole) of N-(2-thiazolyl)-1-phenol-4-sulfonamide, 17.1 Gm. (0.2 mole) of piperidine, and 18 Gm. (0.2 mole) of 37% formaldehyde solution in 200 ml. of methanol, a batch of the 2-(piperidinomethyl)-N-(2-thiazolyl)-1-phenol-4-sulfonamide was prepared in essentially the same manner as described above. The crude product, about 70 Gm., was then suspended in dimethylformamide. To the resulting suspension, was added an excess (42.5 Gm., 0.5 mole) of piperidine and 37% formaldehyde solution (45 Gm., 0.5 mole). The resulting reaction mixture was stirred and heated on the steam bath for four hours. At this time the mixture was poured into about 750 ml. of water. The precipitate which formed was aged in the chillroom overnight, filtered, washed with water, and dried; weight of product, 15 Gm. (14.6% yield). More product was in the mother liquor but was not worked up. The crude bis-Mannich base was purified by dissolving it in hot chloroform (*ca.* 50 ml.) and filtering the solution. To the clear filtrate was added 500 ml. of petroleum ether causing the product to separate from the solution. The resulting precipitate was aged in a chillroom and filtered. More product was obtained by concentration of the filtrates; yield, 12.5 Gm. (11.8%).

Anal.–Calcd. for $C_{21}H_{30}N_4O_3S_2$: N, 12.43; S, 14.23. Found: N, 12.02; S, 14.29.

The 2,6-di-(piperidinomethyl)-N-(2-thiazolyl)-1-phenolsulfonamide (10 Gm.; 0.019 mole) was converted to the corresponding dihydrochloride by treating with an excess of concentrated hydrochloric acid in about 100 ml. of isopropanol. The product was isolated by distilling off the solvents *in vacuo*. The residue was purified by dissolving it in hot dimethylformamide (*ca.* 20 ml.) and precipitating the product by addition of an excess of a 50:50 mixture of petroleum ether and isopropanol (*ca.* 200 ml.). The product was aged in the chillroom for two hours, filtered, and dried *in vacuo;* yield, 8 Gm. (68% conversion). It melted (decompn.) in the range of 184–191°.

Anal.–Calcd. for $C_{21}H_{32}Cl_2N_4O_3S_2$: C, 48.17; H, 6.16; Cl, 13.54; N, 10.70; S, 12.25; mol. wt., 523.5. Found: C, 48.33; H, 6.96; Cl, 13.68; N, 10.72; S, 11.78; mol. wt., 540 (determined by differential vapor pressure thermistor method).[3]

Procedure C.—This procedure illustrates the preparation of a bis-phenolsulfonamide Mannich base of the type described by structural formula D and exemplified by the preparation of compound IV.

N,N' - Di - [N -(2 - thiazolyl) - 5 - sulfonamido - 2-hydroxybenzyl]-piperazine, IV.—To 400 ml. of methanol was added 104 Gm. (0.4 mole) of N-(2-thiazolyl)-1-phenol-4-sulfonamide, 38.8 Gm. (0.2 mole) of piperazine hexahydrate, and 36 Gm. (0.4 mole) of 37% formaldehyde to form complete solution. After the solution had been stirred and heated on a steam bath for about five minutes, a cloudiness appeared and an oily product began to separate from the solution. The mixture was permitted to stir one hour and then was cooled to room temperature. The crude product was dissolved in 600 ml. of dimethylformamide with the aid of gentle warming of the steam bath. The solution was treated with a large excess (4,800 ml.) of acetone. The mixture was stirred well and permitted to stand in the chillroom overnight. The crystals which separated were filtered, washed with two 100-ml. portions of acetone, and dried. Several more crops of crystals separated from the mother liquor on standing. These were filtered and dried; total yield, 62.5 Gm. (50.2%); m. p. 178–185° (decompn.).

Anal.—Calcd. for $C_{24}H_{26}N_6O_6S_4$: C, 46.29; H, 4.21; N, 13.50; S, 20.59. Found: C, 45.84; H, 4.48; N, 13.15; S, 20.49.

Synthesis of the Hydrochloride Salts

Procedure D.—The preparation of compound IIA represents a typical conversion of the free base of a Mannich derivative of a phenolsulfonamide to the corresponding hydrochloride salt.

2 - (Piperidinomethyl) - N - (2 - thiazolyl) - 1-phenol-4-sulfonamide hydrochloride, IIa.—To 1 Gm. (0.0028 mole) of 2-(piperidinomethyl)-N-(2-thiazolyl)-1-phenol-4-sulfonamide was added 20 ml. of isopropanol. Into the resulting mixture was bubbled hydrogen chloride gas. At first the solid dissolved in the solution but then the hydrochloride began to separate. The flask was chilled well in an ice bath to permit complete separation of the hydrochloride salt. It was filtered, washed a few times with small portions of isopropanol, and dried. The hygroscopic product was recrystallized by dissolving it in a small portion of methanol-ethanol and precipitating with an excess of anhydrous ether. The mixture was permitted to stand in the chillroom overnight. The product which separated from the mixture was filtered and dried; yield, 0.54 Gm. (50%); m. p. 185–189° (decompn.).

Anal.—Calcd. for $C_{15}H_{20}ClN_3O_3S_2$: C, 46.20; H, 5.17; Cl, 9.09; N, 10.78; S, 16.45. Found: C, 46.23; H, 5.38; Cl, 8.83; N, 10.59; S, 16.23.

Synthesis of the Acetyl Derivatives

Procedure E.—The preparation of compound Ib represents an example of a procedure for preparing a mono-acetyl derivative of these Mannich phenolsulfonamides.

Acetyl Derivative of 2-(4-Morpholinomethyl)-N-(2-thiazolyl)-1-phenol-4-sulfonamide, Ib.—To 3.55 Gm. (0.01 mole) of 2-(4-morpholinomethyl)-N-(2-thiazolyl-1-phenol-4-sulfonamide was added 1.47 ml. (0.014 mole) of acetic anhydride, 1.6 ml. (0.02 mole) of pyridine, and 10 ml. of acetone. The mixture was stirred until nearly all of the solid was in solution (about five minutes) and then the mixture was heated to about 50° under reflux. At this time some precipitation occurred. The mixture was permitted to stand at 40° for thirty minutes and was then placed in the chillroom. To the mixture was then added 10 ml. of an ice cold 3% ammonia solution, with a few ice chips. The precipitate was filtered and washed with 10 ml. of 1% ammonia solution, followed by 10 ml. of water, and then 3 ml. of ethanol. The product was dried at 56° for one hour; yield, *ca.* 1 Gm. (25%); m. p. 165–167° (decompn.).

Anal.—Calcd. for $C_{16}H_{19}N_3O_5S_2$: C, 48.35; H, 4.82; N, 10.57; S, 16.13; acetyl value, 10.8; mol. wt., 397.5. Found: C, 48.89; H, 5.19; N, 10.37; S, 15.95; acetyl value, 10.7; mol. wt. by Menzies-Wright method, 403.

[3] This method was presented by A. Wilson, *et al.*, at the American Chemical Society Meeting-in-Miniature, Seton Hall, East Orange, N. J., January 1959.

TABLE II.—*In Vitro* ANTIBACTERIAL AND ANTIFUNGAL STUDIES[a,b]
Minimal Inhibitory Concn. γ/ml.

No.	Compound	*Trichophyton mentagrophytes* E-11	*Sarcina lutea* ATCC 9341	*Bacillus subtilis* ATCC 6633	*Proteus vulgaris* STCC 8427	*Salmonella gallinarum* Led. An. Ind. 604
I	2-(4-Morpholinomethyl)-N-(2-thiazolyl)-1-phenol-sulfonamide	...[c]	250 62[d]	...	125	125[d]
Ia	Hydrochloride	...	250	250	250	250
Ib	Acetyl derivative	...	...	...	...	...
II	2-(Piperidinomethyl)-N-(2-thiazolyl)-1-phenol-sulfonamide	...	250 62[d]	...	250 62[d]	...
IIa	Hydrochloride	...	125	...	125	...
IIb	2,6-Bis compound dihydrochloride	...	250 62	250	250	...
III	2-(Pyrrolidylmethyl)-N-(2-thiazolyl)-1-phenol-sulfonamide	...	250	...	...	...
IIIa	Hydrochloride	...	...	...	...	...
IV	N,N′-di-[N-(2-thiazolyl)-5-sulfonamido-2-hydroxybenzyl] piperazine	62 8[d]	...	250	...	...
IVa	Dihydrochloride	...	...	...	...	...
V	2-(N-Methylpiperazinomethyl)-N-(2-thiazolyl)-1-phenol-4-sulfonamide	...	...	...	125[d]	...
Va	Dihydrochloride	...	250	...	125[c]	...
VI	2-(Diethylaminomethyl)-N-(2-thiazolyl)-1-phenol-4-sulfonamide	...	250 62[d]	...	...	...
VIa	Hydrochloride	...	...	...	...	...
VIb	Acetyl derivative	250	...	...	...	...
VII	2-(Dimethylaminomethyl)-N-(2-thiazolyl)-1-phenol-4-sulfonamide	250	125[d]	...	...	...
VIIa	Hydrochloride	...	...	...	...	...

[a] Test bacteria against which the compounds showed no activity include: *Mycobacteriums megmatis, Staphylococcus aureus, Pseudomonas aeruginosa,* and *Escherichia coli.* [b] Test fungi against which the compounds showed no activity include: *Candida albicans, Saccharomyces carlsbergensis, Mucor ramannianus, Fusarium episphaeria, Hormodendrum cladosporoides, Microsporum gypseum, Botrylis cinerea, Penicillium digitatus, Myrothecium verrucaria, Alternaria fasciculata,* and *Aspergillus fumigatis.* [c] Test compound inactive at highest test level used, namely, 250 mcg./ml. [d] Partial inhibition.

BACTERIOLOGICAL STUDIES

Antibacterial and Antifungal *In Vitro* Studies.—Representative types of compounds from this series of Mannich base derivatives of phenolsulfonamides were placed in the *in vitro* antibacterial and antifungal screening program. The special bacteriological media (Mueller-Hinton) for sulfonamides (containing no *p*-aminobenzoic acid) was used for these studies. As the data given in Table II indicates, the antibacterial properties of these compounds are not particularly impressive. Some activity was demonstrated by most candidate compounds against at least one or two of four bacteria, namely: *Sarcina lutea* (ATCC 9341), *Bacillus subtilis* (ATCC 6633), *Salmonella gallinarum* (LAI 604)$_3$, and *Proteus vulgaris* (ATCC 8427), from a total of eight test organisms. The minimal inhibitory concentration of these compounds in terms of γ/ml. required, however, was fairly high in each case, indicating a relatively low order of activity in all cases. A study of Table I will show that the candidate compounds showing activity against the greatest number of bacteria (three or four) are I, Ia, and IIb.

Against approximately twelve test fungi used for screening purposes, three of the compounds tested namely: IV, VIb, and VII, demonstrated some activity against one fungus, *Trichophyton mentagrophytes* (Ell). Of these compounds IV exhibited fairly good antifungal activity being inhibitory at 62 γ/ml. and showing partial inhibitance at 8 γ/ml. However this piperazine derivative failed to show any significant activity against the other test fungi. Although not indicated in the table, compound IVa did show partial inhibitory action against *Candida albicans* at 125 γ/ml.

Antibacterial *In Vivo* Studies.—None of the representative candidate compounds tested exhibited any appreciable activity in *in vivo* antibacterial studies.

Virological Studies.—None of the representative candidate compounds tested exhibited any antiviral activity against virus organisms, namely, Columbia S. K. and Influenza A (PR 8).

Pharmacological Studies.—Representative types of the phenolsulfonamide Mannich bases and their derivatives were submitted for preliminary pharmacological, gross observation studies in mice. None of the compounds tested exhibited any interesting symptomatology in these screening tests.

Several of the compounds (I, Ib, II, IV, and Va) prepared in this series were tested for any potential oral hypoglycemia activity. All of these compounds proved to be inactive in this respect.

Parasitological Studies.—With the knowledge that certain piperazines have demonstrated effective action against certain types of parasites, particularly certain species of roundworms, pinworms, hookworms, etc., strongly infecting domestic animals (6), several Mannich bases of this series, in which a piperazine molecule was substituted into the phenolsulfonamide nucleus, namely, compounds IV, IVa, V, and Va, were submitted for parasitological screening. These compounds were tested against *Schistosoma mansoni* (blood flukes) in mice at 100 mg./Kg., orally, twice daily for five days, and found to be inactive.

The same compounds were also inactive against *Nematospiroides dubius* (intestinal helminths) in mice.

SUMMARY

1. The synthesis of eight Mannich bases, derived from N-(2-thiazolyl)-1-phenol-4-sulfonamide and related hydrochlorides and acetyl derivatives, has been described.

2. Representative candidate compounds of this series were tested. With the exception of some slight antibacterial and antifungal activity (*in vitro*) these compounds failed to demonstrate any biological properties of significant interest.

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Rate of Release of Medicaments from Ointment Bases Containing Drugs in Suspension

By TAKERU HIGUCHI

An equation relating the rate of release of solid drugs suspended in ointment bases into perfect sinks is derived. The final expression is found to be surprisingly simple and convenient.

IN AN EARLIER publication (1) an equation was given relating the amount and rate of release of materials suspended in an ointment base to time and variables of the system

$$Q = (2A - C_s)\sqrt{\frac{Dt}{1 + \frac{2(A - C_s)}{C_s}}}$$

where Q = the amount absorbed at time t per unit area of exposure, A = the concentration of drug expressed in units/cm.^{3}, C_s = the solubility of the drug as units/cm.^{3} in the external phase of the ointment, and D = the diffusion constant of the drug molecule in the external phase.

The present communication is concerned with the theoretical derivation of this relationship. Normally, diffusional calculations are extremely complex and lead to unwieldy expressions. In the present instance, despite the obvious complexity of the type of system involved, the equation comes out rather simply and in a useful form.

The equation is derived for a system described as follows: (*a*) the suspended drug is in a fine state such that the particles are much smaller in diameter than the thickness of the applied layer; (*b*) the amount of drug, A, present per unit volume is substantially greater than C_s, the solubility of the drug per unit volume of the vehicle; (*c*) the surface to which the drug ointment is applied is immiscible with respect to the ointment and constitutes a perfect sink for the released drug.

All of the above conditions are evidently self apparent, except possibly for the reference to a perfect sink. In the publication cited above it was pointed out that the rate of absorption of drug from an ointment could be effectively limited by any one of the three processes involved: (*a*) drug clearance below the "barrier layer," (*b*) passage through the "barrier layer," or (*c*) release by the ointment itself.

It was shown that in the cases where either of the first two processes were rate limiting, only the thermodynamic activity of the drug in the base was important. If the last process is of paramount importance, then we are tacitly assuming that the surface to which the ointment is applied acts as a perfect sink.

DERIVATION OF THE EQUATION

For such a system we can draw a concentration profile which may exist after the lapse of finite time after application of the ointment (Fig. 1). The solid line in the diagram would essentially represent the concentration gradient existing after time, t, in the ointment layer normal to the absorbing surface. The total drug concentration, as indicated in the drawing, would be expected to show a more or less sharp discontinuity at distance h from the surface, none of the suspended phase dissolving until the environmental concentration drops below C_s. The sharpness of the break will be largely a func-

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