N-(NICOTINAMIDO-METHYL)-SULPHONAMIDES

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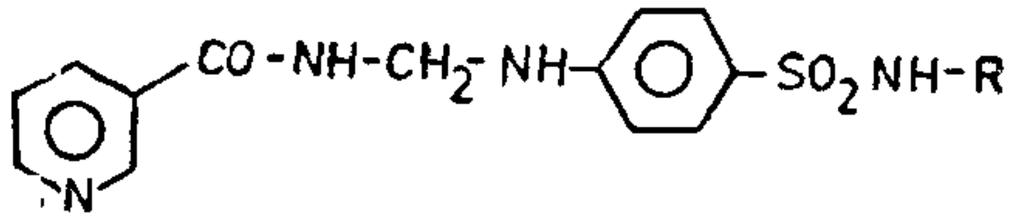
ABSTRACT

N-hydroxymethylnicotinamide has been condensed with sulphanilamide, sulphathiazole, sulphadiazine, sulphamerazine and sulphasomidine to form Mannich bases N^4-(Nicotinamido-methyl)-sulphonamides, whose structures have been confirmed by analytical, UV, IR and NMR data. All these Mannich bases are more antibacterial than their respective parent sulpha as indicated by bacteriostatic tests.

INTRODUCTION

ALIPHATIC[1] and heterocyclic secondary amines[1,2] have been widely used in Mannich reaction[3,4], but aromatic amines[4,5] and some sulphonamides containing anilino $-NH_2$ group have been used to a very limited extent. KUTLU[6] has condenced sulphonamides in Mannich reaction through hydroxymethylation of succinamide.

In spite of the recent broad spectrum antibiotics sulphonamides are still the drugs of importance. Therefore Mannich bases (I) of a few sulphonamides have been synthesized to see how far the activities of sulphonamides are modified.



(I)

EXPERIMENTAL

Melting points (uncorrected) were observed using hot stage microscopic melting point apparatus. Ultraviolet and infrared spectra were recorded on Parkin–Elmer spectrophotometers models 202 in dioxane and 237 in KBr respectively (Table I). NMR spectra were recorded on 60 MHz Varian spectrophotometer and chemical shifts were recorded in τ values.

N-Hydroxymethyl nicotinamide was prepared after the method of Crechelsk[7], by refluxing a mixture of nicotinamide (·01 mol), aqueous solution of 37% formaldehyde (·012 mol) and anhydrous potassium carbonate (·05 mol) for half an hour and cooled at 0° C for 5–6 hours, when the product separated as a white crystalline compound.

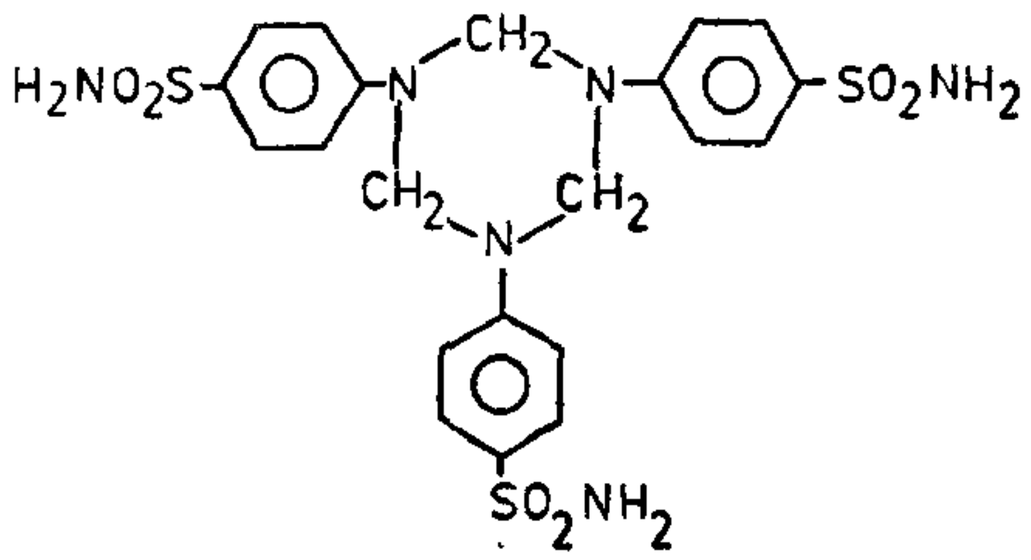
Mannich bases were synthesized by refluxing ·01 mol each of N-hydroxymethyl nicotinamide and the respective sulphonamides in rectified spirit in presence of hydrochloric acid. After refluxing for nearly two hours, about 50% of the solvent was removed by distillation and the remaining solution on keeping at 5° C for 3 to 4 days gave the Mannich bases (I), which were recrystallized with suitable solvent.

Antibacterial Test (*With S. H. Mishra*)

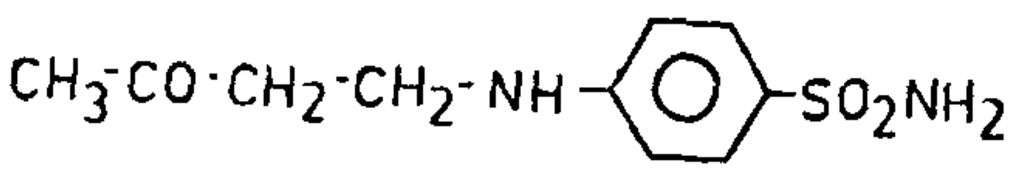
The antibacterial activity was tested after the method of Maruzzella and Henry[8]. The samples and standards (sulphonamides) were prepared by dissolving 20 mg of the compounds in 1 ml of 5% dimethyl formamide. Bacteriological oxoid nutrient agar medium was distributed in sterile 10 cm petridishes and allowed to cool on a level surface. These petridishes were inoculated with 2 ml fresh broth culture of the respective organisms and after incubating for 24 hours at 37° C, were used for test. Whatmann filter paper No. 1 discs of 6 mm diameter were used (Table II).

DISCUSSION

Gerhard Siewart[9] has shown that sulphanilamide very quickly reacts with aqueous formaldehyde to form a derivative of anhydroformaldehyde aniline derivative (II) and later on, under suitable conditions of reaction, formaldehyde, sulphanilamide and acetone at pH 3 gave Mannich bases (III).



(II)



(III)

Singh *et al.*[10] showed that sulphanilamide reacted with formaldehyde solution and hydrogen of N^1 nitrogen, due to its high protonation tendency was involved to form (IV).

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TABLE I

Sl. No.	Compound	Crystallization solvent yield %	M.P. °C formula	Elemental analysis Found. C H N Reqs. (C H N)			$\lambda_{max.}$ nm	Characteristic bands* IR cm^{-1}		
1.	N-hydroxymethyl-nicotinamide	Acetone 80	141 $C_6H_6N_2O$	55·05 (55·26)	5·20 5·26	18·35 (18·42)	285	3400 m 1445 m	2900 s 710 w	1660 m
2.	N^4-(Nicotinamido methyl)-sulphanilamide	Dioxane +Water 56	221–23 $C_{13}H_{14}N_4SO_3$	50·52 (50·98)	4·45 4·58	18·22 (18·30)	271	2360 w 1450 m	2920 w 710 m	1660 m
3.	N^4-(Nicotianamido methyl)-sulphathiazole	Petro. Ether + Benzene 47	245 $C_{16}H_{15}N_5S_2O_5$	49·02 (49·36)	4·21 3·88	17·45 (17·99)	272	3360 w 1455 m	2920 w 710 m	1670 m
4.	N^4-(Nicotianamido methyl)-sulphadiazine	Abs. Alcohol 68	220 · $C_{17}H_{16}N_6SO_3$	53·00 (53·13)	3·92 4·17	21·96 (21·88)	314	3380 w 1440 m	2925 w 710 w	1670 m
5.	N^4-(Nicotinamido methyl)-sulphamerazine	Dioxane +Water 71	231 $C_{18}H_{19}N_6SO_3$	53·82 (54·27)	4·20 4·52	21·02 (21·11)	309	3380 w 1440 m	2925 w 710 w	1670 w
6.	N^4-(Nicotinamido methyl)-sulphasomidine	Solvent Ether + Benzene 51	241 $C_{10}H_{21}N_6SO_3$	55·88 (55·34)	4·23 4·58	20·29 (20·39)	309	3360 w 1435 w	2910 w 710 m	1680 w

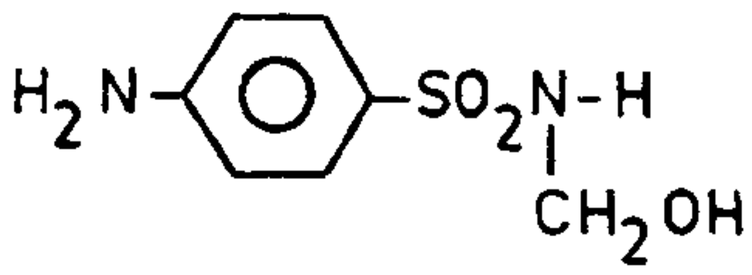
* 3,400 cm^{-1} –OH frequency band, 3370 ± 10 cm^{-1} N–H of SO_2NH, 3075 ± 5 cm^{-1} SO_2NH–R, 2925 to 2900 cm^{-1} C–H stretching frequency of CH_2, 1670 ± 10 cm^{-1} > CO absorption of sec. amide 1445 ± 10 cm^{-1} C–H deformation of CH_2, 710 cm^{-1} out of plane N–H deformation of sec. amide.

TABLE II

Compounds	Zone of inhibitation (in mm)					
	B. anthracis	*E. coli*	*B. subtilis*	*P. aeruginosa*	*C. pyogenes*	*S. aureus*
N^4 (Nicotinamido methyl)-sulphanilam de	24	18	18	18	18	18
Sulphanilam de	16	18	18	14	14	14
N^4 (Ni otinam do m thyl)-sulphathiazole	20	22	22	24	26	24
Sulphathiazole	20	22	24	24	22	24
N^4 (Nicotinamido m thyl)-sulphadiazine	14	14	12	14	12	16
Sulphadiazine	17	18	16	20	16	18
N^4 (Nicotinamido methyl)-sulphamerazine	18	20	20	22	20	20
Sulphamerazine	20	18	16	14	14	20
N^4 (N cot.namidomethyl)-sulphasomidine	24	22	22	20	24	22
Sulphasomidine	22	24	26	26	22	24
Control*	..	..	..	..	..	..

* Control = Blank; Dimethyl formamide 5%.

To avoid ambiguity of the reaction of sulphonamides, we first prepared N-hydroxymethylnicotinamide, which readily condensed with sulphonamides and formed (I), involving N^4 hydrogen, which was confirmed by negative diazo reaction.



(IV)

The analytical results recorded in Table I support the structures (I), which have been confirmed by electronic and IR spectral data. All Mannich bases show an absorption band at $3440 \pm 10\ cm^{-1}$ of weak or medium intensities corresponding to alkyl aryl amine[11], $-CH_2-NH-C_6H_4-$, indicating the involvement of anilino $-NH_2$ group in the reaction. In addition, the anilino absorption at $3180\ cm^{-1}$ weak or medium present in the parent sulphas disappears in the Mannich bases. Absorption bands $3365 \pm 15\ cm^{-1}$ and $3075 \pm 5\ cm^{-1}$ of weak to strong intensities observed in parent sulphas[12,13] as also in Mannich bases show that the group SO_2NH remains intact, other characteristic bands due to > CO, –CO–NH– and $-CH_2-$ are given in Table I itself. Besides, the Mannich bases show characteristic frequencies of six membered heterocyclic pyridine[14] and the respective sulphonamides[13].

NMR spectra further confirmed the structures (I). The signals at 3·12 to 3·32 τ (multiplet) for protons of aromatic rings; 6·64 to 7·08 τ with an integral of 4H (multiplet) for protons of $-NH-CH_2-NH-$, 2·00 to 2·43 τ for protons of pyridine ring and 1·7 τ for proton of $-SO_2NH-$ have been observed in the NMR spectra of the Mannich bases.

In general all Mannich bases (weight for weight) of sulphonamide moiety have shown enhanced antibacterial activity.

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1. Horning, *Organic Synthesis Collective*, John Wiley and Sons Inc., New York, 1955, Vol. 3, 305.
2. Tramontini, M., "Advances in the chemistry of mannich bases," *Synthesis*, 1973, p. 1.
3. Blick, F. F., *Organic Reactions*, John Wiley and Sons, Inc. New York, 1942, Vol. **1**, 303.
4. Thompson, B. B., *J. Pharm. Sci.*, 1968, **57**, 715.
5. Licart, J. J., Hartzel, L. W., Gregy–Dougherty and Benson, F. R., *J. Amer. Chem. Soc.*, 1955, **73**, 5386.
6. Kutlu, H., *J. Fac. Pharm. Istanbul.*, 1973, **9**, 23; 1975, **11**, 1; 1975, **11**, 5; 1976, **12**, 176.
7. Bozenna, C. and Tadeusz, U., *Roczniki. Chem.*, 1953, **27**, 396.
8. Maruzzella, J. C. and Henry, P. A., *J. Amer. Pharm. Assoc.*, 1958, **47**, 471.
9. Gerhard Siewart, *J. Prakt. Chem.*, 1962, **17**, 121.
10. Singh, G. B., Dixit, B. B. and Vijjan, V. K., *J. Indian Chem. Soc.*, 1968, **45**, 262.
11. Russell, R. A. and Thompson, H. W., *J. Chem. Soc.*, 1955, p. 483.
12. Bellamy, L. J., *Infrared Spectra of Complex Molecules*, Chapman and Hall, London, 1975, p. 407.
13. Chaturvedi, K. K. and Kaushal, R., *Indore Univ. Res. J. Sci.*, 1972, **1**, 56; 1972, **1**, 75. Gupta, R. R. and Kaushal, R., *J. Indian Chem. Soc.*, 1974, **51**, 385.
14. Katritzky, A. R., *Quort. Rev.*, 1959, **13**, 358.

A NOTE ON THE APPLICATION OF HILBERT TRANSFORM FOR THE TRANSFORMATION OF GEOMAGNETIC ANOMALIES DUE TO TWO-DIMENSIONAL BODIES

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ABSTRACT

In the magnetic method of geophysical prospecting, the anomalous magnetic field of the earth is measured choosing either the vertical, the total or the horizontal field magnetometer. Interpretation of the anomalous field may be carried out in a number of ways which can be improved if the measurements in two or three components are available. Geological structures such as sheet-like bodies, dykes, faults, etc., causing magnetic anomalies, may be approximated to be two-dimensional. For two-dimensional bodies, it is shown here that the magnetic anomaly in any one component can easily be transformed into the other by means of Hilbert transform. The relations for such transformations, derived using a thin sheet model are presented here. These relations are applicable for magnetic anomalies over all two-dimensional bodies.

INTRODUCTION

IT is the usual practice in magnetic prospecting to take measurements of the anomalous magnetic field of the earth choosing one particular component (total, vertical or horizontal) of interest. The magnetic anomaly thus measured is interpreted in terms of subsurface geological structures assumed to be responsible for the anomaly. Magnetic interpretation can be carried out in several ways and may be improved if the measurements are available in two or three components[6]. Geological structures such as dykes, thin sheets, faults, etc., extending infinitely in the strike direction are generally approximated to two-dimensional bodies. For two-dimensional bodies, the magnetic anomaly in the vertical and the horizontal components form a Hilbert transform pair[1]. Hence, the magnetic anomaly in the vertical (horizontal) component can be obtained from the horizontal (vertical) component using Hilbert transform. For two-dimensional bodies it is shown here that the magnetic anomaly in any component can be transformed into the other using the fundamental relationship among them and the Hilbert transform. The relations for computing these components are derived using a thin sheet model. These relations are applied on a field example.

THEORY

Let there be a thin sheet (Fig. 1), extending infinitely along its strike and is magnetized due to induction only. The expressions for the vertical (ΔV), horizontal (ΔH) and total (ΔT) field magnetic anomalies