Synthesis and Biological Activity of Some N-(3-Methoxy-4-hydroxy) Benzylidene Substituted Diphenylamine-2-Carboxylic acid Hydrazides and their Mannich bases:

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Summary: Twenty new C-Mannich bases of N-(e-methoxy-4-hydroxy)-benzylidene-substituted diphenylamine-2-carboxylic acid hydrazides have been synthesised from different primary aromatic amines and various N-(3-methoxy-4-hydroxy)benzylidene substituted-diphenylamine-2-carboxylic acid hydrazides, synthesised from substituted diphenylamine-2-carboxylic acid hydrazides and vanillin, in the presence of formalin under Mannich conditions for the evaluation of their antibacterial and antiviral activities.

Diphenylamine-2-carboxylic acid hydrazides have been reported to be associated with a wide range of biological activities[1-5], such as antibacterial, antiviral antifungal, antitubercular and anti-inflammatory. Studies on the N-benzylidene derivatives of substituted diphenylamine-2-carboxylic acid hydrazides[6] have revealed that among these compounds, N-(3-methoxy-) benezylidene-5-chloro-diphenylamine-2-carboxylic acid hydrazides (2, R^1 = Cl) showed the inhibition of extent of 98, 95 and 48 % *in vitro* and 53, 74 and 65 % in vivo with the substituent R as 2-CH_3, 3-CH_3 and 2-OCH_3 respectively against Gomphrene Mosaic virus (GMV) also. These compounds have been shown to possess significant antibacterial properties[6], and Mannich bases have also been reported as antimicrobial agents[7,8]. Thus it was considered of interest to synthesize different N-benezylidene derivatives of diphenylamine-2-carboxylic acid hydrazides and their Mannich bases.

The present communication deals with the synthesis of 2(R'=H, R=H 2-CH_3, 3-CH3 and 2-OCH_3) from (1) and vanillin) and (3) from (2) and different aromatic amines in presence of formalin (40 %) under Mannich conditions (Scheme 1) with the view to observe the biological response of these compounds having dechlorinated diphenyl amine moiety and a methylene linkage (5-CH_2-NH-3) therein. Structures of all the synthesized compounds were confirmed by their sharp IR stretching bands at 3300 cm^{-1} (-NH), 1620 cm^{-1} (CONH), 1590 cm^{-1} (HC=N-) and 2950 cm^{-1} (-CH_2-) NMR of the compound no. 5 in Table-2 showed prominent peak at 4.70 π (1H, N-CH), 6.25 π (3H, OCH_3) 7.85 π (3H, CH_3) 2.0-3.8 π (15H, ArH, 2H-Ar-NH-Ar, Ar-NH, both exchangeable on D_2O' shake),5.82π (2H-CH_2) Methylene linkage at the position ortho to phenolic group as specified in the scheme was confirmed by the D_2O shake of N.M.R.,spectra 0.3π (1H, CONH, broad singlet exchangeable with D_2O), 2.1 π (1H, OH sharp singlet exchangeable with D_2O).

Hence, the possibility of the methylene linkage in 3b, the other alternative position is ruled out. Further it has been reported[11] that the positions, ortho and para to the phenolic group are active for Mannich reaction. But, in this case, as para position is not free, the reaction will take place at the ortho position. So the structure (3a) is confirmed.

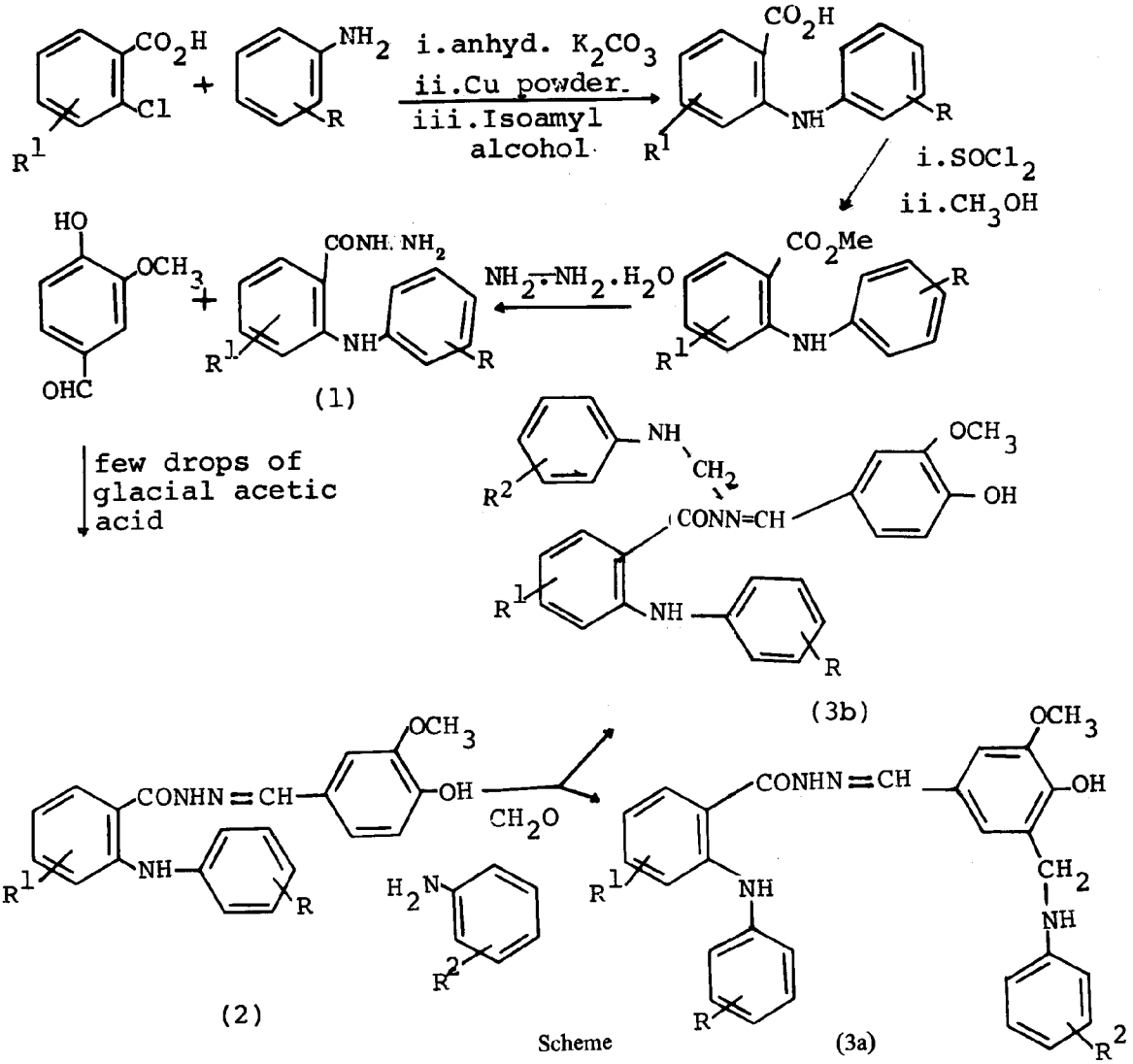
Pharmacological studies

(i) Antibacterial activity:- All the compounds of table 1 and 2 were screened for their inhibitory effect against *B. subtilis S. aureus, E. coli* and *S. typhi* by the following method of Varma and Nobles[10]. It was observed that none of these compounds displayed any significant activity' against any strain with the conclusion that this activity was almost lost with the removal of chlorine in the diphenylamine moiety and addition of an arylaminomethyl group at 5 position in the benzylidene portion of the molecule (3a).

(ii) Antiviral activity:- Compound No.1 of table 1 and six compounds of Table 2 (3, 4, 11, 14, 15, 20) were tested for their antiviral activity *in vitro* against *Tobacco mosaic* virus (TMV) *Nicotiana tobaccum* var. Burley Ky[58] and the % inhibition caused by these compounds was observed to be 50, 10, 50, 40, and 11 respectively with the conclusion that:-

(a) The substitution of an arylamine methylgroup in the benzylidene part of the molecule (2) reduced the inhibition.

Synthesis of Compounds : The compounds were synthesized by the following route (Scheme).1



Scheme

(b) Presence of the methyl group in the diphenylamine moiety further reduced the inhibition.

(c) The presence of a chloro group at position-5 in the diphenylamine moiety could be essential for the significant activity in the series of the compounds.

Experimental

The melting points were determined in open capillaries and are uncorrected IR sepctra in KBr were recorded on Perkin-Elmer 137G. Spectrometer (ν max. in cm^{-1}) and NMR sepctrum in $CDCl_3$ on a varian A-90D instrument using TMS as internal standard (chemical shift in τ ppm). The purity of the compounds was checked on T.L.C. substituted diphenylamine-2-carboxylic acid hydrazides were prepared according to the published procudre.[9]

N-(3-Methoxy-4-Hydroxy-)benzylidene-substituted diphenyl-2-carboxylic acid hydrazides (2)

A mixture of diphenylamine-2-carboxylic acid hydrazides (2.27 g, 0.01 mole) and vanillin (1.52 g, 0.01 mole) in ethanol (50 ml) containing 3 drops of glacial acetic acid was refluxed on a water bath for 4 hrs. The solid separated on cooling was filtered

Table 1. N-(3-Methyoxy-4-hydroxy)-benzylidene substituted diphenylamine-2-carboxylic acid hydrazides (2)

Compound No.	R	R^1	Molecular formula	m.p. °C	% Analysis N Calcd.	Found
1.	H	H	$C_{21}H_{19}N_3O_3$	200	11.63	11.50
2.	2-CH_3	H	$C_{22}H_{21}N_3O_3$	214	11.20	10.95
3.	3-CH_3	H	$C_{22}H_{21}N_3O_3$	190	11.20	11.00
4.	2-OCH_3	H	$C_{22}H_{21}N_3O_4$	200	10.74	10.55

Yield – Compounds were obtained in 70-80% yields.

Table. 2. N-(3-Methoxy-4-hydroxy-5-arylaminomethyl) benzylidene diphenylamine-2-Carboxylic acid hydrazides (3a)

Compound No.	R^2	Molecular formula	m.p. °C	% analysis N Calcd.	Found
	R and R^1 = H				
1.	C_6H_4.CH3 (p)	$C_{29}H_{28}N_4O_3$	135	11.66	11.42
2.	$C_6H_4.OCH_3$ (p)	$C_{29}H_{28}N_4O_4$	125	11.29	11.15
3.	C_6H_4. COOH (p)	$C_{29}H_{26}N_4O_5$	130	10.98	10.85
4.	$C_6H_4.NO_2$ (o)	$C_{28}H25N_5O_5$	196	13.98	13.48
5.	$C_6H_4.CH_3$ (m)	$C_{29}H_{28}N_4O_3$	137	11.66	12.36
6.	$C_6H_4.COOH_2H_5$ (p)	$C_{31}H_{30}N_4O_5$	168	10.40	10.28
7.	C_6H_4.Cl (p)	$C_{28}H_{25}N_4O_3Cl$	180	11.20	11.24
	R=2-CH_3 R^1=H				
8.	$C_6H_4.CH_3$ (p)	$C_{30}H_{30}N_4O_3$	108	10.98	10.72
9.	C_6H_4. CH_3 (p)	$C_{30}H_{30}N_4O_4$	105	10.98	10.68
	R=3-CH_3, R^1=H				
10.	$C_6H_4.CH_3$ (m)	$C_{30}H_{30}N_4O_3$	108	10.98	10.72
11.	$C_6H_4.NO_2$ (m)	$C_{29}H_{27}N_5O_5$	160	14.24	13.40
12.	C_6H_4.COOH (p)	$C_{30}H_{28}N_4O_5$	110	10.98	10.72
13.	$C_6H_4.CH_3$ (p)	$C_{30}H_{30}N_4)_3$	70	10.64	10.70
	R=2-OCH_3, R,=H				
14.	$C_6H_4.CH_3$ (p)	$C_{30}H_{30}N_4O_4$	105	10.98	10.75
15.	$C_6{}_3$ $(NO_2)_2$(o,p)	$C_{29}H_{26}N_6O_8$	120	14.24	14.22
16.	$C_6H_4.CH_3$ (p)	$C_{30}H_{30}N_4O_4$	100	10.98	10.72
17.	C_6H_4. OCH_3 (p)	$C_{30}H_{30}N_4O_5$	105	10.64	10.52
18.	$C_6H_4.COOC_2H_5$ (p)	$C_{31}H_{32}N_4O_6$	110	9.86	9.76
19.	C_6H_4. COOH (p)	$C30H_{28}N_4O_6$	107	10.39	10.10
20.	$C_6H_4.NO_2$ (m)	$C_{29}H_{27}N_5O_6$	98	10.84	10.56

Yield – Compounds were obtained in 60-65% yield.

washed and recrystallised from ethanol (2). Thus prepared are given in Table-1.

N (3-Methoxy-4-Hydroxy-5-arylamino-methyl)-benzylidene substituted diphenylamine-2-carboxylic acid hyrazides (3a)

In a typical reaction, to a mixture of 2(R=H, 3.61 g, 0.01 mole) and p-toluidine (1.07 g, 0.01 mole) in ethanol (50 ml) was added 40% formalin (0.75 ml 0.01 mole) and the contents were refluxed on a water bath for 6 hrs. and was left overnight the separated solid was filtered, washed and recrystallised

from ethanol (3). Thus synthesized are given in Table-2.

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