Asian Journal of Chemistry Vol. 22, No. 8 (2010), 5987-5992

Synthesis, Characterization and Pharmacological Evaluation of Some Novel 3,6-Dinitrocarbazole Derivatives

RAVI TIWARI* and GURMEET CHHABRA
SVKM'S, NMIMS University, School of Pharmacy and Technology Management, Shirpur Campus, Shirpur-425 405, India
E-mail: ravisun4@rediffmail.com

N-Mannich bases of newly synthesized carbazole compounds were synthesized from carbazole by reacting with series of aldehydes *i.e.*, formaldehyde and acetaldehyde and the various secondary amines. Synthesized compounds were characterized by spectral studies and evaluated for antibacterial activities by cup and plate method. The statistical analysis was done by students "t" test and the values were expressed as mean ± SEM.

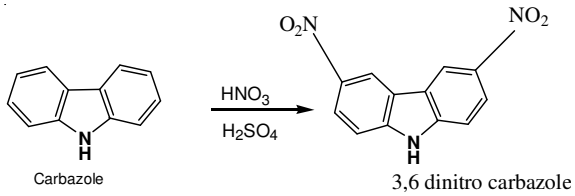
Key Words: N-Mannich bases, 3,6-Dinitrocarbazole, Antibacterial.

INTRODUCTION

Mannich reaction is the condensation between a compound containing at least one active hydrogen atom, with a primary and secondary-amine to form Mannich-base[1]. The drugs with carbazole moiety were found to possess antiinflammatory, analgesic, antibiotic, insecticidal, fungicidal[2], neuroleptic, anti HIV[3], anticancer and antiyeast activities. Due to the above mentioned significance of carbazole moiety we opted to synthesize various N-substituted 3,6-dinitrocarbazole and to evaluate their antibacterial activities.

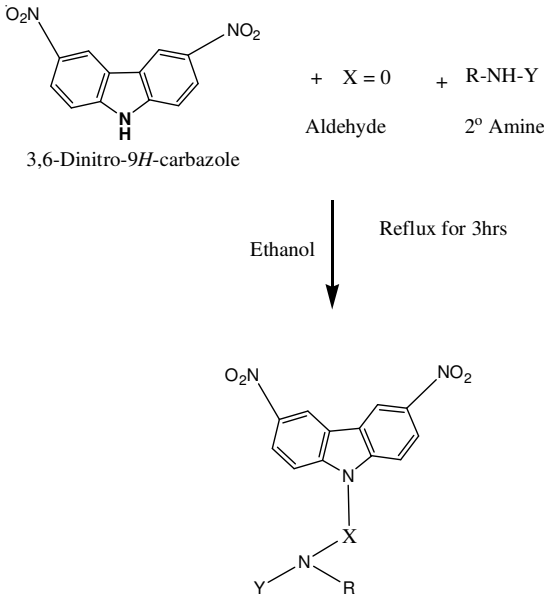
EXPERIMENTAL

Melting points were determined by open-ended capillary tube in the electrical melting point apparatus and are uncorrected and the purity of the compounds were checked by TLC using silica gel as stationary phase and the spots were visually detected in an iodine chamber. The structure of the synthesized compounds was elucidated by FT-IR4 (Shimadzu-8400 series) in KBr disc[4] and FT ^{1}H NMR[5] (Brucker 400 MHz) in DMSO-d_6.



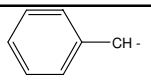
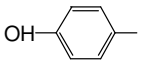
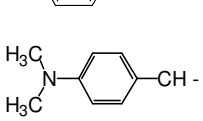
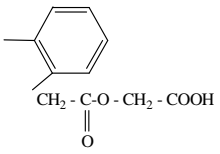
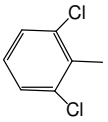
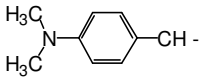
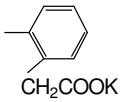
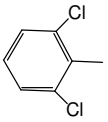
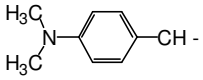
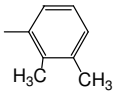
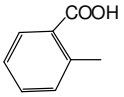
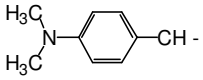
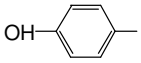
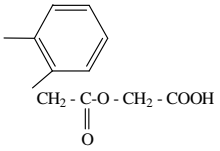
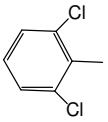
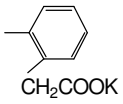
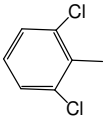
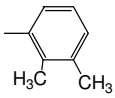
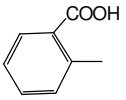
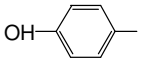
Carbazole 3,6 dinitro carbazole

Scheme-I



Scheme-II

Comp. code	X		R
NAA	CH_3CH-	CH_2 - C-O - CH_2 - COOH (O)	Cl, Cl
NAD	CH_3CH-	CH_2COOK	Cl, Cl
NAM	CH_3CH-	H_3C, CH_3	COOH
NAP	CH_3CH-	-$COCH_3$	OH
NBA	CH -	CH_2 - C-O - CH_2 - COOH (O)	Cl, Cl
NBD	CH -	CH_2COOK	Cl, Cl
NBM	CH -	H_3C, CH_3	COOH

NBP		-$COCH_3$	
NDA			
NDD			
NDM			
NDP		-$COCH_3$	
NFA	HCH		
NFD	HCH-		
NFM	HCH-		
NFP	HCH-	-$COCH_3$	

Synthesis of 3,6-dinitrocarbazole: Dissolve carbozole (0.02 M) in glacial acetic acid (0.08 M) slightly warm to dissolve completely. To the solution add conc H_2SO_4 (0.15 M) with vigorous stirring. Immerse the flask in ice and bring temperature to 3 ºC. Add drop wise from a dropping funnel a precooled mixture of conc HNO_3 (0.02 M) and H_2SO_4 (0.01) with vigorous stirring. Temperature should never be allowed to rise above 10 ºC. After the addition is complete, allow the beaker to stand at room temperature for 0.5 h. Pour the contents of flask into 150 g of crushed ice. Nitrocarbazole precipitate out, filter and wash thoroughly with water. Recrystallize with chloroform (**Scheme-I**).

Preparation of N-Mannich bases of 3,6-dinitrocarbazole[6]: Equimolar quantities (0.01 mol) of 3,6-dinitrocarbazole and secondary amine were dissolved in methanol (30 mL) in a beaker under perfect ice cold condition and stirred constantly and then 0.01 mol of series of aldehyde (such as formaldehyde and acetaldehyde) was added slowly and heated to reflux for 3 h. The content was kept over night in the freezer.

TABLE-2
SPECTRAL DATA OF NEWLY SYNTHESIZED
3,6-DINITROCARBAZOLE DERIVATIVES [Ref. 4]

Comp. code	m.p. (ºC)	R_f value	IR spectra (cm^{-1})	^1H NMR spectra
NAA	195-200	0.73	3417, 1716, 3050, 1449, 1497, 570, 750, 2359, 1497	7.22-7.68 (m, Ar-H), 3.49 (s, CH_2), 8.10 (d, OH), 4.8 (CH), 3.14 (CH_2), 1.18 (CH)
NAD	208-215	0.45	3417, 2922, 3050, 1450, 571, 750, 2362, 1599, 1514	7.42-7.84 (m, Ar-H), 1.15 (s, CH), 3.18 (s, CH_2), 1.68 (s, CH_3), 2.54 (s, CH_3)
NAM	155-160	0.61	3417, 1649, 3035, 1511, 751, 2361, 1649, 1552	6.69-8.1 (m, Ar-H), 2.4 (s, CH_3), 1.25 (s, CH_3), 6.66 (CH), 9.15 (OH)
NAP	220-222	0.78	3417, 1329, 1449, 1650, 1378, 773, 1513	7.23-8.11 (m, Ar-H), 2.16 (s, CH_3), 6.8 (d, CH) 4.8 (OH), 1.57 (s, CH_3)
NBA	230-237	0.59	3416, 600, 3048, 752, 720, 1733, 1599	7.33-7.88 (m, Ar-H), 2.28 (s, CH_2), 6.11 (s, CH)
NBD	210-220	0.52	3416, 1641, 637, 1469, 781, 2361, 1447	6.69-8.1 (m, Ar-H), 2.77 (s, CH_2), 6.66 (CH).
NBM	190-195	0.91	3413, 1649, 3050, 1450, 751, 1331, 2359, 1503	7.05-8.15 (m, Ar-H), 2.33 (s, CH_3), 9.2 (S, OH) 6.2 (CH)
NBP	159-162	0.82	3418, 1350, 1684, 1450, 750, 1511, 3033	7.15-8.34 (m, Ar-H), 2.15 (s, CH_3) 2.53 (OH), 6.79 (CH)
NDA	182-187	0.79	3417, 1543, 1450, 813, 1323, 570, 1739, 1699, 2921, 1543	6.97-7.3 (m, Ar-H), 3.05 (CH_2), 3.95 (CH_2), 7.4-8.1 (CH)
NDD	135-140	0.69	3417, 3051, 570, 2920, 1449, 750, 1329, 1713, 1512	7.26-7.43 (m, Ar-H), 3.5 (CH_2), 2.16 (CH_3), 8.06-8.2 (CH)
NFP	190-192	0.91	3326, 1366, 2353, 1651, 3050, 1452, 751	7.15-7.98 (m, Ar-H), 2.28 (CH_3), 7.69 (CH), 9.23 (OH)
NDM	192-197	0.84	3418, 1650, 2921, 1450, 751, 2360, 1508	7.07-8.10 (m, Ar-H), 2.18 (CH_3), 9.2 (OH), 2.34 (CH_3), 6.1 (CH)
NDP	210-216	0.90	3418, 1451, 749, 1331, 1654, 1371, 1555	7.20-8.09 (m, Ar-H), 2.19 (CH_3), 3.09 (CH_3), 6.7 (CH), 9.73 (OH)
NFA	190-193	0.67	3418, 1700, 3049, 1452, 571, 750, 2356, 1539	7.02-8.3 (m, Ar-H), 6.35 (CH_2), 6.65 (CH)
NFD	195-197	0.78	1614, 2361, 1498, 3049, 751, 600, 1447	7.2-7.5 (m, Ar-H), 2.1 (CH_2), 5.7 (CH_2), 8.07-8.10 (CH)
NFM	191-193	0.87	3345, 1651, 1445, 1473, 767, 2359, 1498	7.09-8.3 (m, Ar-H), 6.42(CH), 2.56 (CH_3)

The product obtained was recrystallized from chloroform (**Scheme-II**). The percentage yield, R_f value, melting point and spectral data were given in Table-1.

Antibacterial activity [Cup and Plate method][7]: Peptone, beef extract and sodium chloride were dissolved in purified water and the pH of the media was adjusted to 8.4 with 5 M sodium hydroxide solution. To this solution agar was added, boiled and stirred thoroughly until the agar was dissolved. Then 5-20 mL of this nutrient agar medium was transferred into each boiling tube and plugged with non-absorbent cotton. The tubes containing the nutrient agar medium were sterilized by pressure controlled heat sterilization technique using an autoclave at 15 Ibs and 115 ºC for 20 min. After the sterilization the nutrient agar medium was melted, cooled and inoculated with G (+ve) organism *viz*. *Bacillus subtilis* and G (-ve) organism *viz*. *E. coli* and poured into sterile Petri dish to get a uniform thickness of 5-6 mm. Cups were made out in the other plate using sterile cork borer (6 dm).

The standard antibacterial agent amikacin (10 µg/mL) and solvent control (10 % v/v Tween 80) suspension and the series of the newly synthesized nitrocarbazole derivatives (100 µg/mL) were added with the sterile micro pipette into each cup. The plates were kept in the refrigerator for 6 h and then incubated at 37 ºC for 24 h and the diameter of zone of inhibition were measured[7].

TABLE-2
ANTIBACTERIAL DATA OF SYNTHESIZED COMPOUNDS

S. No.	Compound code	Zone of inhibition (mm)	
		E. coli	*B. subtilis*
1	Control	0	0
2	Std Amikacin	17	17
3	**NAA*****	7	11
4	**NAD*****	11	4
5	**NAM****	6	3
6	**NAP****	6	3
7	**NBA****	6	8
8	**NBD*****	12	3
9	**NBM****	5	7
10	**NBP*****	4	11
11	**NDA*****	6	10
12	**NDD*****	10	4
13	**NDM**	5	3
14	**NDP*****	5	15
15	**NFA**	4	10
16	**NFD*****	10	3

***Indicates highly significant. **Indicates moderately significant.

RESULTS AND DISCUSSION

A series of 16 novel 3,6-dinitrocarbazole derivatives were synthesized and elucidated by spectral data and evaluated their antibacterial activities. Compound **NFD, NDA, NDP, NBP** and **NAA** shows highly significant antibacterial activity. Compound

NFP, NFM, NBM and **NBA** shows moderate antibacterial activity. Compounds **NDF, NDD, NDM, NBD, NAP, NAD** and **NAM** showed low antibacterial activity against *Bacillus subtilis* at 100 mg^3/mL. The compounds **NFD, NDD, NBD** and **NAD**, showed significant antibacterial activity and compounds **NFM, NDA, NBA, NAP, NAM** and **NAA** showed moderate antibacterial activity (Table-2). The compounds **NFP, NFA, NDP, NDM, NBP** and NBM showed low antibacterial activity against *E. coli* at 100 mg^3/mL.

REFERENCES

1. C. Mannich and W. Krosche, *Arch. Pharm.*, **250**, 647 (1912).
2. L. Govindasamy, V. Rajakannan, D. Velmurugan, A.K. Mohanakrishnan and P.C. Srinivasan, *Cryst. Res. Tech.*, **38**, 182 (2003).
3. T. Vandana and K.J. Rajendra Prasad, *Indian J. Chem.*, **42B**, 3131 (2003).
4. R.M. Silverstein, F.X. Webster and D. J. Kiemle, Spectrometric Identification of Organic Compounds, John Wiley & Sons, Inc., edn. 6 (1998).
5. P. Ertl, Novartis-Molinspiration Software Programme.
6. A.C. Moffat, Clark's Isolation and Identification of Drugs, The Pharmaceutical Press, edn. 2, pp. 1106-1109 (1986).
7. S.K. Kulkarni, Handbook of Experimental Pharmacology, Vallabh Prakashan, edn. 3, 125 (1987).

(*Received*: 17 September 2009; *Accepted*: 30 April 2010) AJC-8651

INTERNATIONAL CONFERENCE "TOPICAL PROBLEMS OF ORGANOMETALLIC AND COORDINATION CHEMISTRY" (V RAZUVAEV LECTURES)

3 — 9 SEPTEMBER, 2010

NIZHNY NOVGOROD, RUSSIA

Contact:
Dr. Viacheslav Kuropatov
G.A. Razuvaev Institute of Organometallic Chemistry of RAS
Nizhny Novgorod, Tropinina str., 49, Russia
Tel: +7 8314 627682; Fax.: +7 8314 627497
E-mail: razuvaev2010@iomc.ras.ru; ash@iomc.ras.ru
Website: http://razuvaev2010.iomc.ras.ru/