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Synthesis and Biological Activities of Some New Formazans, Part-I

S.D. BHARADWAJ
Cancer Hospital & Research Institute, Gwalior-474 009, India

1-(Phenyl-3-(2-methoxy-4-N,N′-bis-2′-cyanoethylamino phenyl) *p*-tolyl formazans have been synthesised by first reacting 4-N,N′-bis-2-cyanoethylamino-2-methoxy benzaldehyde with *p*-tolyl hydrazide which gave the acid hydrazone. The acid hydrazone on treatment with diazotised aromatic amines in pyridine medium furnished fifteen formazans in 40 to 54% yield. The acid hydrazone and the formazans were found to be devoid of anticancer and anti-HIV activities.

Key words: Synthesis, Biological activities, Formazans.

INTRODUCTION

Formazans are used as dyes[1, 2] and belong to azo dye[2] family and as chelating agents[3]. Synthesis, antiviral[4], antimicrobial[5, 6] and anti-inflammatory[7] activities of formazans have been given in literature. Some products from 2-methyl-4-N,N′-bis-2′-cyanoethylaminobenzaldehyde have shown anticancer activity which prompted the use of these aldehydes for synthesis of new formazans. Recently Jolly and others[8, 9] have synthesised new formazans for assessing their antiviral, anticancer activity[10, 11] and anti-HIV activities[12].

The present study records the reaction of 4-N,N′-bis-2-cyanoethylamino-2-methoxy benzaldehyde[9] **(I)** with *p*-tolyl hydrazide[13] **(II)** which gave the acid hydrazone **(III)**. The acid hydrazone on treatment with diazotised aromatic amines in pyridine medium furnished formazans **(IV)** (Table-1). The reaction sequence has been outlined in Scheme-I.

EXPERIMENTAL

Preparation of *p*-methyl benzhydrazide (*p*-tolylhydrazide)

Methyl *p*-toluate: Methyl ester of *p*-toluic acid was readily prepared by refluxing a mixture of *p*-toluic acid (27.2 g, 0.2 mole), absolute methanol (80 mL) and concentrated sulphuric acid (4 mL) for 4 h heat on steam bath and worked up as for methyl *p*-chlorobenzoate. The ester was crystallised from petroleum ether (60°–80°C); m.p. 35°C; yield about 70%.

Hydazide: Methyl *p*-toluate and hydrazine hydrate dissolved in methanol (25 mL) was refluxed for 30 min on a hot water bath. On cooling, a white compound was obtained which was crystallised from aqueous ethanol as very light small leaflets; m.p. 116–117°C; yield about 70%.

Synthesis of *p*-tolyl hydrazone of 2-methoxy-4-N,N′-bis-2′-cyanoethyl-aminobenzaldehyde: Solutions of 2-methoxy-4-N,N′-bis-2′-cyanoethylamino-benzaldehyde (2.57 g, 0.01 mole) in ethanol (5 mL) and *p*-tolyl hydrazide (1.5 g, 0.01 mole) in ethanol (5 mL) were mixed and the mixture was refluxed for 15 min. On cooling, the liquid hydrazone separated as solid. It was filtered under suction and recrystallised from rectified spirit; m.p. 180°C; yield 98%.

Molecular formula $C_{22}H_{23}N_5O_2$, Analysis: found C 64.2, H 6.4, N 20.0%; required C 67.86, H 5.91, N 17.99%.

IR-spectra were recorded on Perkin-Elmer model 1720 and FTIR infracord spectrophotometer. The product shows IR bands, ν(N—H) 3325–3320, ν(C=O) 1680–1670, ν(C=N) 1610-1600, ν(N=N) 1570–1560, ν(C—N) 1350–1330, ν(C—OH) 3500 cm^{-1}.

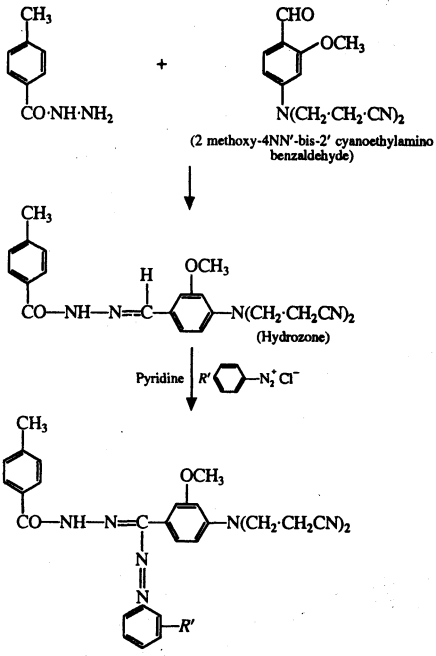
Synthesis of 1-(phenyl-3-(2-methoxy-4-N,N′-bis-2′-cyanoethylamino-phenyl)-*p*-tolyl formazans: Aniline (0.46 g, 0.01 mole) was dissolved in aqueous hydrochloric acid (4 mL 1 : 1). The contents were cooled and aqueous sodium nitrite (0.3 g in 2 mL water) was slowly added; 2-methoxy-4-N,N′-bis-2′-cyanoethylaminobenzalidine-*p*-tolyl hydrazone (0.49 g, 0.01 mole) was dissolved in dry pyridine (10 mL) and sodium acetate (0.3 g) was added. The contents were cooled in an ice bath and stirred. The solution of benzene diazonium chloride was added dropwise for 30 min, maintaining low temperature (0°C). The reaction mixture was kept in an ice bath for 4 h and then poured with stirring in ice water. The resulting dark brown coloured solid was washed with water till free from pyridine, filtered under suction and dried. The product was crystallised from ethanol; m.p. 160°C; yield 50%; colour brown.

Molecular formula $C_{28}H_{27}N_7O_2$. Analysis: found C 70.00, H 6.70, N 18.00%; required C 68.15, H 5.47, N 19.8%.

The product shows IR bands, ν(N—N) 3325–3320, ν(C—O) 1680–1670, ν(C—N) 1610–1600, ν(N=N) 1570–1560, ν(C—N) 1350–1330, ν(C—OH) 3500 cm^{-1}.

Anticancer activity: Six formazans (Nos. 3, 4, 9, 10, 11, 13) and one hydrazone (No. 1) were tested for their anticancer activity. None of the products was found active at the dose level tested.

Anti-HIV activity: Six formazans (Nos. 3, 4, 9, 10, 11, 13) and one hydrazone (No. 1) have been assessecl under *in vitro* anti-HIV activity. All the compounds (seven) did not show significant activity. Tests were conducted at National Cancer Institute, Maryland, USA.



1phenyl-3(2 methoxy-4NN'-bis-2'-cynoethylamino phenyl *p*-tolyl formazans.)

Scheme-1

TABLE-1
PHYSICAL DATA OF FORMAZANS

S.No.	—R′	Yield (%)	m.p. (°C)	Colour
1.	Hydrazone	65	180	light yellow
2.	H	50	160	deep brown
3.	CH_3 (*o*)	54	170	deep brown
4.	CH_3 (*m*)	50	170	light yellow
5.	CH_3 (*p*)	48	170	deep brown
6.	Cl (*o*)	40	145	brown
7.	Cl (*m*)	40	135	deep brown
8.	Cl (*p*)	40	140	deep brown
9.	OCH_3 (*o*)	50	165	deep brown
10.	OCH_3 (*m*)	40	150	deep brown
11.	OCH_3 (*p*)	45	165	light yellow
12.	NO_2 (*o*)	45	122	deep brown
13.	NO_2 (*m*)	55	125	deep brown
14.	NO_2 (*p*)	40	120	deep brown
15.	COOH (*o*)	55	175	white
16.	COOH (*p*)	50	165	yellow

All compounds gave satisfactory elemental analysis; solvent for crystillisation: ethanol.

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