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Synthesis, Anti-HIV and Anticancer Activities of Some New Formazans

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1-(Phenyl-3-(2-methyl-4-NN′-bis-2′-cyanoethyl-aminophenyl) 5-chlorosalicylformazans have been synthesised by first reacting 2-methyl-4-NN′-bis-2′-cyanoethylamino-benzaldehyde with 5-chlorosalicylhydrazide which gave respective acidhydrazone. The acidhydrazone on treatment with diazotised aromatic amines in pyridine medium furnished formazans in 30 to 85% yield. Three derivatives of the formazans have been prepared by the reaction of the formazans with acylchlorides under Schotten-Baummanm reaction conditions.

INTRODUCTION

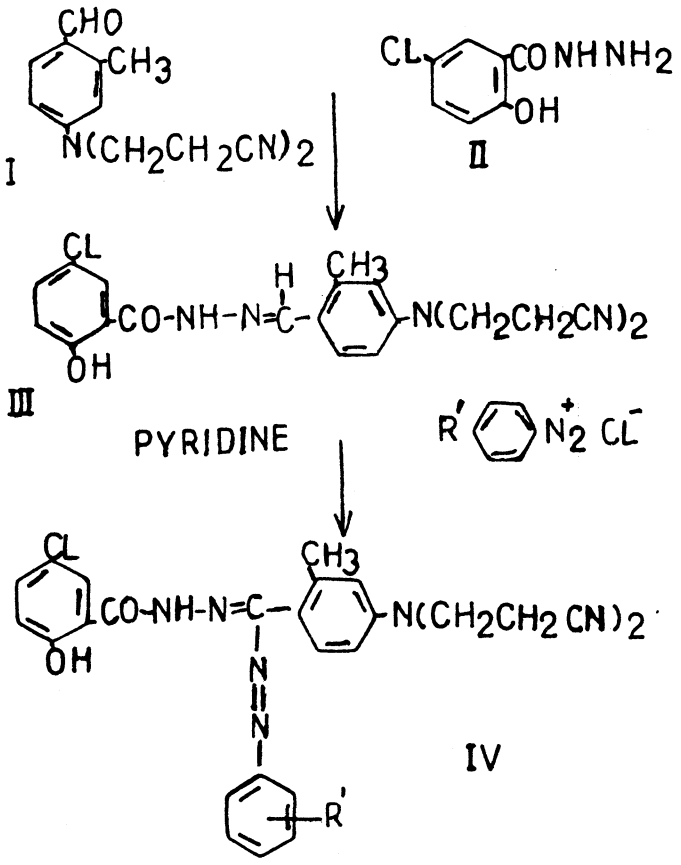
Formazans belong to azo dye family[1] and have mostly been used as dyes[2,3]. Fibre reactive formazan dyes having chloro/fluoro pyrimidine groups are used for dyeing and printing[4]. Synthesis, antiviral[5], antimicrobial[6,7] and antiinflammatory[8] activities of formazans have been given in literature. Hydrazones of benzaldehyde and salicylaldehyde have been screened for their activity against a large number of micro-organisms[9]. Application of formazan in testing sensitivity of anti-cancer drugs has been mentioned by Hongo and co-workers[10].

Literature survey has revealed that cyanoethylated aldehydes and 3-methoxy-4-allyloxybenzaldelyde have not been exploited for the synthesis of formazans. Their products such as imidazolones, Schiff bases have been claimed to possess high degree of anti-cancer, anti-HIV and anti-microbial activities. Recently Jolly and co-workers[11,12] have synthesised new formazans for assessing their antiviral activity. Some products from 2-methyl-4-NN′-bis-2′-cyanoethylaminobenzaldehyde have shown anticancer activity which prompted the use of these aldehydes for the synthesis of new formazans.

The present study records the reaction of 2-(methyl-4-NN′-bis-2′-cyanoethylaminobenzaldehyde[12] (I) and 5-chlorosalicylhydrazide (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

5-Chlorosalicylhydrazide and 2-methyl-4-NN′-bis-2-cyanoethylaminobenzaldehyde were prepared by procedures given in the literature.



SCHEME I

Synthesis of 5-chloro-salicylhydrazone of 2-methyl-4-NN'-bis-2'-cyanoethyl-aminobenzaldehyde.

Solution of 2-methyl-4-NN'-bis-2'-cyanoethylaminobenzaldehyde (2.41 g, 0.01 mole) in ethanol (5 mL) and 5-chlorosalicylhydrazide (1.86 g, 0.01 mole) in ethanol (5 mL) were mixed and the mixture was refluxed for 15 min. On cooling the liquid the hydrazone separated as solid. It was filtered under suction and recrystallised from rectified spirit. m.p. 200°C, yield 98%. Analysis: found (%) C 61.8, H 5.0, N 17.06, Cl 9; required C 61.4, H 4.8, N 17.0 Cl 8.8; IR: (C═O) 1670–1660 cm^{-1}, ν(N—H) 3325–3320 cm^{-1}, ν(N═N) 1580–1570, ν(C—N) 1380–1350 cm^{-1} and ν(C═N) 1610–1600 cm^{-1}, ν(OCH_3) 2820–2810 cm^{-1}, ν(C—OH) 3500 cm^{-1}

TABLE-1
PHYSICAL DATA OF FORMAZANS

S.No.	R′	Yield %	m.p. (°C)	Colour
1.	H	70	110	b
2.	CH_3 (*o*)	80	135	db
3.	CH_3 (*m*)	80	144	y
4.	CH_3 (*p*)	85	125	br
5.	Cl (*o*)	65	105	db
6.	Cl (*m*)	50	105	LY
7.	Cl (*p*)	50	190	LY
8.	OCH_3 (*o*)	50	140	LY
9.	OCH_3 (*m*)	80	135	db
10.	OCH_3 (*p*)	50	210	Lg
11.	NO_2 (*o*)	50	95	db
12.	NO_2 (*m*)	30	85	br
13.	NO_2 (*p*)	80	95	b
14.	COOH (*o*)	50	190	LY
15.	COOH (*p*)	60	200	LY
16.	OCH_3 (*p*)	60	140	Lg
17.	CH_3 (*p*)	50	110	b

All compounds gave satisfactory elemental analyses.
Solvent for crystallisation—ethanol.
Brown—b, Dark—d, Light—L, Yellow—Y, Red—r, Green—g.

Synthesis of 1-phenyl-3-(2-methyl-4-NN′-bis-2-cyanoethylaminophenyl)-5-(2 hydroxy-5-chlorobenzoformazan).

Aniline (0.46 g, 0.01 mole) was dissolved in aqueous hydrochloric acid (4 mL, 1 : 1). The contents were cooled and aqueous soldium nitrite (0.3 g in 2 mL water) was slowly added. 2-Methyl-4-NN′-bis-2′ cyanoethylamino-benzylidene-5-chlorosalicyl hydrazide (4.0 g, 0.01 mole) was dissolved in dry pyridine (10 mL) and sodium acetate (0.3 g) was added. The contents were cooled in ice-bath and stirred. Clear and cold solution of benzenediazonium-chloride was added dropwise for 30 min, maintaining low temperature (0°C) . The reaction mixture was kept in ice-bath for 4 h and then poured with stirring in water. The resulting dark-coloured mass was washed with water till free from pyridine, filtered under suction and dried.

The product was crystallised from ethanol. m.p. 110°C, yield 85%. Analysis (%): found C 61.5, H 4.0, N 19.4, Cl 6.9; required (%) C 63.5, H 4.7, N 18.4, Cl 7.06; molecular formula $C_{27}H_{24}{\cdot}N{\cdot}7O_2Cl$. IR: ν(N—H) 3325–3320 cm^{-1}, ν(C=O) 1680–1670 cm^{-1}, ν(C=N) 1610–1600 cm^{-1}, N=N 1570–1560 cm^{-1}, ν(C—N) 1350–1330 cm^{-1}, ν(C—OH) 3500 cm^{-1}.

Most of the compounds are low melting solids of light to dark brown and yellow colour and were obtained in 30 to 85% yield. Formazans are highly soluble in acetone and ethanol.

Formazan-Derivatives A mixture of the formazans (1 g) in aqueous sodium hydroxide (20 mL, 5%) benzoyl chloride (2 mL) was vigorously shaken for 10 min in a boiling tube. When solid separated, it was filtered, dried and crystallised from ethanol. Other derivatives (16, 17, 18) were also prepared by above mentioned procedure.

*Anticancer Activity** Five formazans (Nos. 4, 7, 9, 13, 15) were tested for their anticancer activity. The compound did not show significant anticancer activity.

*Anti-HIV Activity** Five formazans (Nos. 4, 7, 9, 13, 15) and one hydrazone (1) and two derivatives (16, 17, 18) have been tested for anti-HIV activity. The compounds did not show significant activity.

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