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Synthesis of Some Isoindole-1,3-(2H)-dione, Amino-oxy and Biguanidino-oxy Derivatives of Carbazole

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2-(Bromoalkoxy)-1H-isoindole-1,3-(2H)-dione are condensed with carbazole and its derivatives to give ω-N-(carbazol-5-yl) alkoxy 1H-isoindole-1,3-(2H)-diones. Gabriels hydrolysis under acidic conditions give the corresponding amino-oxy salts. Condensation of amino-oxy salts with various *para*-substituted dicyandiamide give corresponding biguanidino-oxy compounds.

INTRODUCTION

The carbazole group of naturally occurring compounds has aroused in the past thirty years considerable interest on account of various aspects of biological activities[1–6]. It therefore seemed desirable to synthesize some amino-oxy and biguanidino-oxy derivatives which may have interesting and improved biological effects.

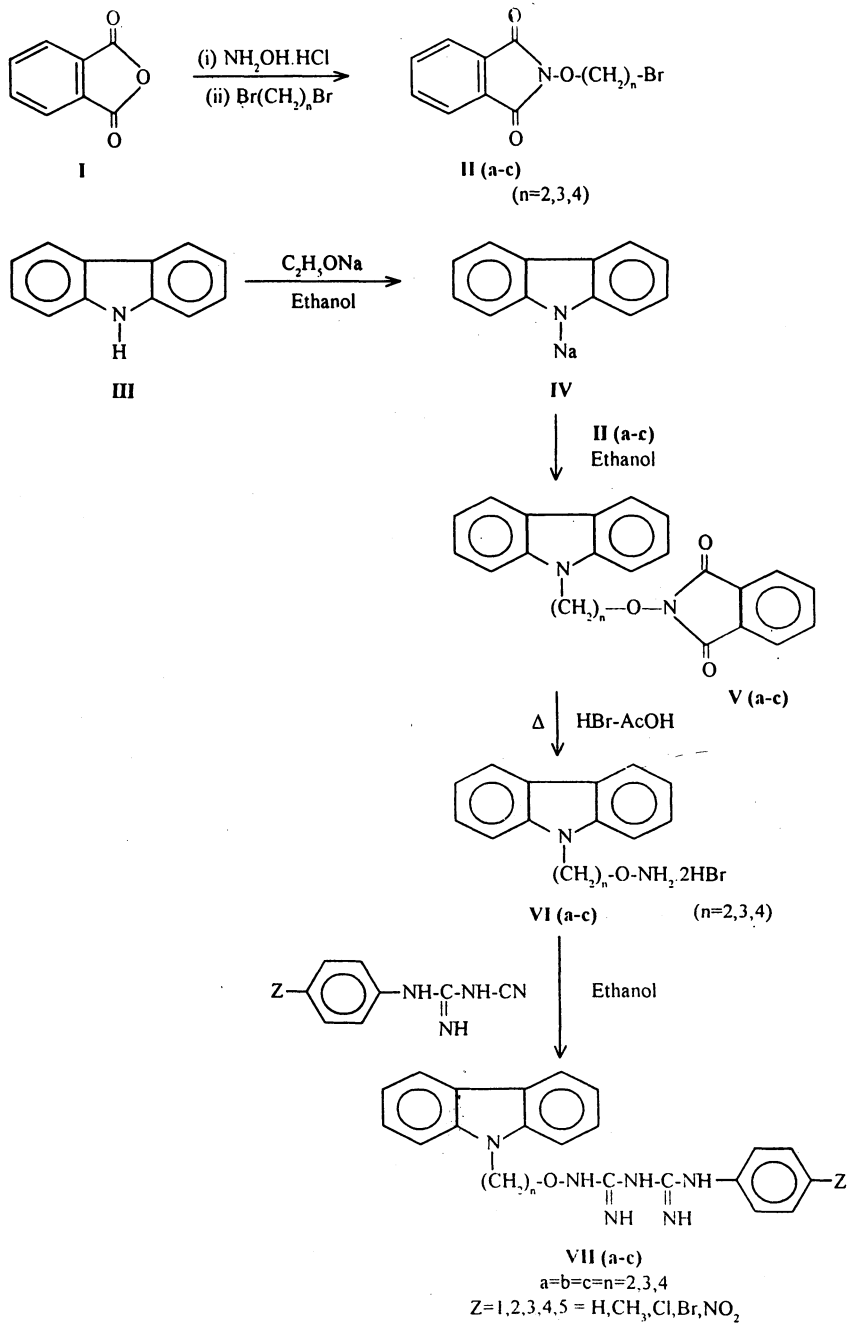
RESULTS AND DISCUSSION

Phthalic anhydride **(I)** was treated with hydroxylamine hydrochloride in presence of sodium carbonate in an aqueous media to give 2-hydroxy-1H-isindole-1,3(2H)-dione[7]. The latter was treated with terminal dibromoalkanes to give 2-(bromoalkoxy)-1H-isoindole-1,3-(2H)-dione (**II**; n = 2,3,4)[8] along with bis compound. Condensation of the sodium salt of carbazole **(IV)** with **(II)** gave ω-N-(carbazol-5-yl) alkoxy-1H isoindole-1,3-(2H)-diones **(Va–c)**. Compounds **(Va–c)** were hydrolysed using HBr/AcOH corresponding amino-oxy **(VI)** salts. Nucleophilic addition of **(VIa–c)** on *para*-substituted dicyandiamide derivative produced corresponding biguanidino-oxy compound of structure **(VIIa–d)**. Dicyandiamide derivatives required for this purpose were prepared by the method of Curd and Rose[9] with some modification and condensed according to the method of Fuller and King[10]. The physical characteristics of all synthesized compounds are presented in Table-1.

IR spectra of compound **V** show weak peak at 1780–1760 cm^{-1} for ν(Co—N—CO), 1301–1244 cm^{-1} for ν(O—N), 1460–1454 cm^{-1} for ν(C=C, Ar). Compound **VI** shows peaks at 3030–2990 cm^{-1} for $\nu(NH_3^+)$ and 2930–2921 cm^{-1} for $\nu(CH_2$ str.). Compound **VII** shows peaks at 1648–1610 cm^{-1} and 1454–1410 cm^{-1} due to C=N stretching of guanidino-oxy group (N—O). Symmetrical stretching appears at 1380–1256 cm^{-1}. Peak at 1362–1290 cm^{-1} is due to (C—N) stretching of (C—NH—C) group.

Molecular ion peaks and fragmentation peaks are given. Phthalimidoxy group shows peaks at 162, 146, 104, 76 as per fragmentation pattern.

Following reaction sequences have been used:



EXPERIMENTAL

All m.p. are uncorrected and determined in open capillaries. Purity of compounds was checked by thin layer chromatography on silica gel in various nonaqueous media. The structure of compounds has been characterised by their micro elemental and spectral studies.

Synthesis of N-hydroxyphthalimide or 2-hydroxy-1H-isoindole-1,3-(2H)-dione

Prepared by already reported method[7].

Synthesis of 2-(bromoalkoxy)-1H-isoindole-1,3-(2H)-dione (II)

Prepared by already reported method[8].

TABLE-1
PHYSICAL DATA OF COMPOUNDS SYNTHESIZED

Comp. No.	m.f.	m.w.	Solvent of crystallisation	m.p. (°C)	Yield (%)	% Nitrogen	
						cal.	obs.
Va	$C_{22}H_{16}N_2O_3$	356	Absolute alcohol	309	55	7.86	7.79
Vb	$C_{23}H_{18}N_2O_3$	370	Absolute alcohol	307	48	7.57	7.41
Vc	$C_{24}H_{20}N_2O_3$	384	Absolute alcohol	320	52	7.29	7.31
VIa	$C_{14}H_{16}N_2OBr_2$	388	Methanol + Chloroform	132	25	7.22	7.27
VIb	$C_{15}H_{18}N_2OBr_2$	402	Methanol + Chloroform	141	27	6.96	6.90
VIc	$C_{16}H_{20}N_2OBr_2$	416	Methanol + Chloroform	147	27	6.73	6.71
VIIa$_1$	$C_{22}H_{22}N_6O$	386	Ethanol + Benzene	241	36	21.76	21.61
VIIa$_2$	$C_{23}H_{24}N_6O$	400	Ethanol + Benzene	237	34	21.00	21.90
VIIa$_3$	$C_{22}H_{21}N_6OCl$	420.5	Ethanol + Benzene	243	37	19.98	19.89
VIIa$_4$	$C_{22}H_{21}N_6OBr$	465	Ethanol + Benzene	248	31	18.06	18.17
VIIa$_5$	$C_{22}H_{21}N_7O_3$	431	Ethanol + Benzene	237(d)	36	22.74	22.79
VIIb$_1$	$C_{23}H_{24}N_6O$	400	Ethanol + Benzene	251	30	21.00	21.09
VIIb$_2$	$C_{24}H_{27}N_6O$	415	Ethanol + Benzene	248	40	20.24	20.11
VIIb$_3$	$C_{23}H_{23}N_6OCl$	434.5	Ethanol + Benzene	255	39	19.33	19.39
VIIb$_4$	$C_{23}H_{23}N_6OBr$	479	Ethanol + Benzene	250	37	17.54	1769
VIIb$_5$	$C_{23}H_{23}N_7O_3$	445	Ethanol + Benzene	247(d)	38	22.02	21.81
VIIc$_1$	$C_{24}H_{26}N_6O$	414	Ethanol + Benzene	253	41	20.29	20.17
VIIc$_2$	$C_{25}H_{28}N_6O$	428	Ethanol + Benzene	258	32	19.63	19.81
VIIc$_3$	$C_{24}H_{25}N_6OCl$	448.5	Ethanol + Benzene	261	31	18.73	18.85
VIIc$_4$	$C_{24}H_{25}N_6OBr$	493	Ethanol + Benzene	259	38	17.04	17.14
VIIc$_5$	$C_{24}H_{25}N_7O_3$	459	Ethanol + Benzene	254(d)	30	21.35	21.22

Preparation of sodium salt of carbazole (IV)

A solution of carbazole and sodium ethoxide in ethanol was stirred while heating on a magnetic stirrer for 6 h. White crystalline heavy solid was formed which changes its colour with time. It was not filtered and used for next step.

Synthesis of ω-N (carbazole-5-yl) alkoxy 1H-isoindole-1,3-(2H)-dione (V)

A suspension of (**IV**) (0.01 mole) and (**II**) (0.01 mole) in ethanol was refluxed on stirrer with heating for 21–27 h. It was filtered, solvent evaporated and the solid obtained was dried and crystallized, m.p. 300–315°C.

Synthesis of amino-oxy alkyl carbazoles salts (VI)

For hydrolysis/dephthaloyllation compound (**VIa–c**) was dissolved in glacial acetic acid and hydrobromic acid was added. The suspension was boiled for 5–10 min. Phthalic acid separated was filtered and the solvent of filtrate was removed under reduced pressure. The solid obtained was crystallized, m.p. 132–147°C.

Preparation of biguanidino-oxy derivatives (VII)

p-Substituted dicyandiamide (0.02 mole) and ω-amino-oxy alkyl carbazole (0.02 mole) were mxed and ethanol (15 mL) was added. The mixture was refluxed for 15–20 h. Dilute solution of $NaHCO_3$ solution was added dropwise. The precipitate obtained was filtered, dried and recrystallized, m.p. 237–259°C.

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