Synthesis and Reactions of New N-[Phthalimido]-Acetoxy and Benzoyloxyphthalimides

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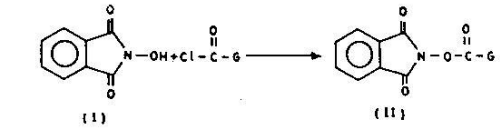
Summary: N-(Phthalimido)acetoxy, o-, m-, and p-benzoyloxy-phthalimides (IIa-d) were newly synthesised. Acid catalyzed ring opening with anhydrous $AlCl_3$ (2 moles) and with excess anhydrous $AlCl_3$ (6 moles) in reactive aromatic substrates were studied.

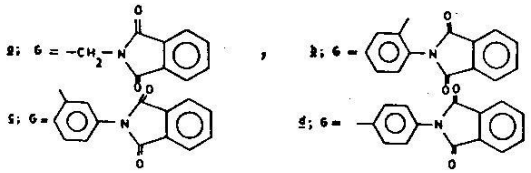
Base catalyzed ring opening with aromatic amines, aminobenzoic acids, hydrazine hydrate and phenyl hydrazine were also studied.

In the present investigation acetoxy-, o-, and p-benzoyloxyphthalimides were introduced in the phthalimide moiety to elucidate their effects on imide rearrangement and ring opening reactions.

N-Hydroxyphthalimide reacted easily with phthalimido-acetyl chloride, o-, m-, and p-phthalimidobenzoyl chlorides [1] to give the corresponding N-(phthalimido)-acetoxy-, o-, m-, and p-benzoyloxyphthalimides (IIa-d).



(I) (II)

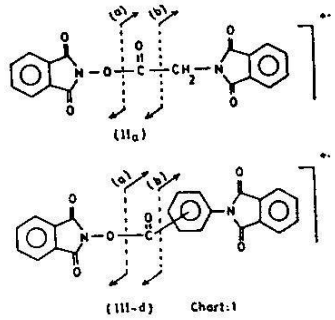


The structure of (IIa-d) was proved from:

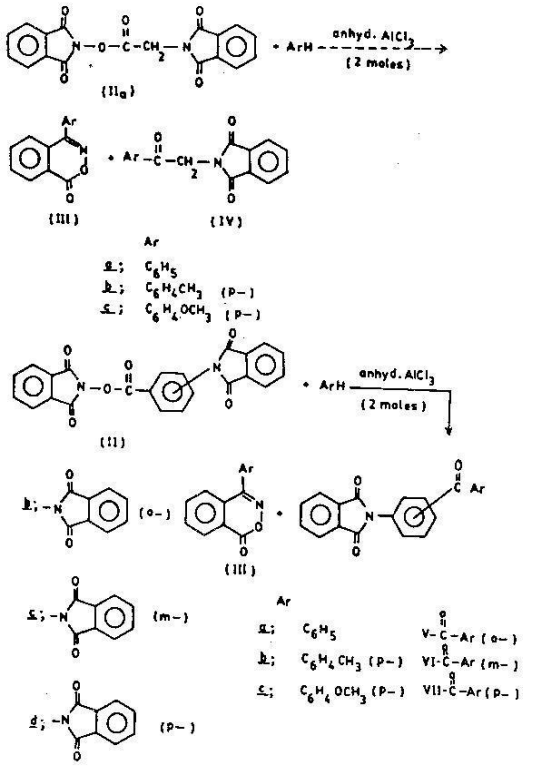
i) IR spectra: which showed νC=O of ester at (1760-1740 cm^{-1}) [2] and doublets in the region (1800-1780 cm^{-1} and 1720-1710 cm^{-1}) as expected for carbonyl groups of cyclic imides [3,4].

ii) ^{1}H-NMR spectra: for (IIa) shows singlet at δ 5.1 ppm corresponding to $-CH_2$ group, and multiplet at δ 7.4-8 ppm corresponding to 8 aromatic protons, for (IIb) shows signals at δ 7.5 to 8.5 ppm corresponding to 12 aromatic protons and for (IId) shows signals at δ 7.4 to 8.4 ppm corresponding to 12 aromatic protons.

iii) Mass spectra: The mass spectra of (IIa and b) gave unstable molecular ions which cannot be detected (cf. Chart 1, Table 1). However (IIc) showed molecular ion [M^+, m/z = 412 (1%)] which undergoes fragmentation via two routes (a, and b) (cf. Chart 1, Table 1), also (IId) showed molecular ion [M^+, m/z = 412 (1%)] which undergoes fragmentation also via two routes (a, and b) (cf. Chart 1, table 1).



(IIa) (IIIa-d) Chart:1



(IIa) (III) (IV) (II) (V-VII)

(IIa-d) undergo acid catalyzed Beckmann rearrangement with anhyd. $AlCl_3$ (2 moles) in reactive aromatic substrates, where (IIa) gave mixtures of 4-aryl-2,3,1-benzoxazones (IIIa-c) and the corresponding aryl-phthalimidomethyl ketones [phenyl-(IVa)-; p-tolyl-(IVb)-; and p-methoxyphenyl -(IVc) phthalimidomethyl ketones]. But (IIb-d) gave the corresponding mixture of 4-aryl-2,3,1-benzoxazone (IIIa-c) and N-(benzoyl phenyl)-phthalimides (V-VII).

The structure of (IIIa-c) was established on the basis of their IR spectra (showing a sharp band at 1750-1730 cm^{-1} characteristic of νC=O of benzoxazones [5], and by their identity with those prepared by the reaction of o-aroylbenzoic acids with hydroxylamine hydrochloride [6].

Similarly, the structure of (IVa-c) was established from: (i) their IR spectra showing νC=O of ketones in the region (1720-1650 cm^{-1}) and coupling νC=O in the region (1780-1760 and 1720-1710 cm^{-1}) [3,4] fo carbonyl bands of cyclic imides. (ii) ^{1}H-NMR spectra of (IVa) shows singlet at δ 5.2 ppm corresponding to 2 protons of $-CH_2$ group, and multiplet from δ 7.5-8.2 ppm corresponding to 9 aromatic protons. (iii) Authentically: by comparison with authentic specimens prepared via the reaction

Table-1: m/z Values followed by % of abundance.

(IIa): 190(1), 188(51), 162(3), 160(100), 147(5), 146(1), 132(7), 104(27), 103(2), 77(18), 76(24), 75(4), 66(7), 51(6), 50(12), 44(3).

(IIb): 266(1), 250(100), 222(8), 162(1), 147(1), 146(1), 132(8), 104(7), 103(1), 77(1), 76(8), 75(1), 60(2), 50(3), 44(1).

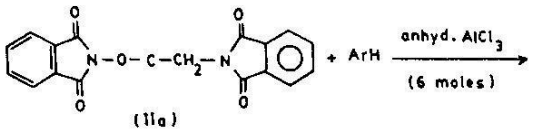
(IIc): 412(1), 266(1), 250(100), 222(4), 162(1), 147(7), 146(1), 132(8), 104(2), 103(3), 77(3), 76(2), 75(4), 60(2), 58(8), 50(8), 44(6).

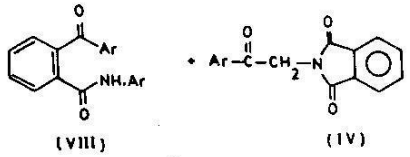
(IId): 412(1), 368(1), 266(2), 250(100), 222(17), 162(1), 147(8), 146(1), 132(10), 104(25), 103(5), 77(35), 76(5), 75(5), 63(4), 52(3), 50(13), 44(7).

of the corresponding acid chlorides with the same aromatic substrates in the presence of anhyd. $AlCl_3$ under the same reaction conditions.

Also the structure of (V-VII) was established on the basis of: (i) Their IR spectra which showed νC=O of ketones in the region (1710-1650 cm^{-1}) and coupling νC=O in the region (1790-1770 and 1720-1710 cm^{-1}). (ii) ^1H-NMR spectra of (VIa) shows signals at δ 7.6-8.1 ppm corresponding to 13 aromatic protons. (iii) Authentically: by direct comparison with authentic specimens prepared via the reaction of the corresponding acid chlorides with the same aromatic substrates in the presence of anhyd. $AlCl_3$ under the same reaction conditions [7].

The reaction of (IIa) with excess anhyd. $AlCl_3$ (6 moles) in the presence of reactive aromatic substrates gave the corresponding mixtures of o-aroyl anilides (VIIIa-c) and phthalimidomethyl ketones (IVa-c). Similarly (IIb-d) reacted with reactive aromatic substrates in the presence of excess $AlCl_3$ (6 moles) to give mixture of o-aroyl anilides (VIIIa-c) and N-(benzoylphenyl)phthalimides (IV-V).



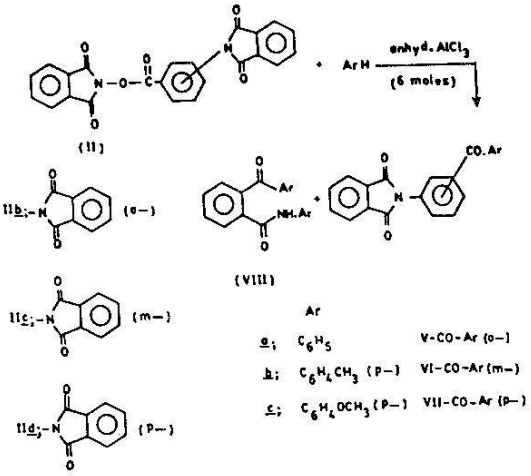


Ar

a; C_6H_5

b; $C_6H_4CH_3$ (P-)

c; $C_6H_4OCH_3$ (P-)



Ar

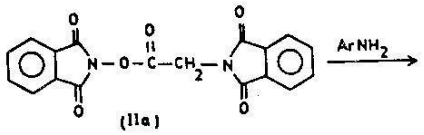
a; C_6H_5 V-CO-Ar (o-)

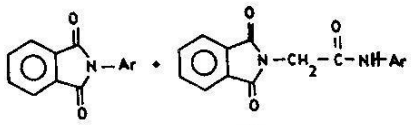
b; $C_6H_4CH_3$ (P-) VI-CO-Ar (m-)

c; $C_6H_4OCH_3$ (P-) VII-CO-Ar (P-)

The structures of (VIIIa-c) were established from: (i) IR spectra which shows νC=O of ketone (1740-1680 cm^{-1}) and νNH of anilide (3440-3220 cm^{-1}). (ii) Authentically [4]: by comparison with authentic samples.

In the present investigation aromatic amines and/or aminobenzoic acid reacted with (IIa) to give the corresponding mixture of N-aryl phthalimides (IXa-g) and N-phthalimido acetanilides (Xa-g)





Ar

a; C_6H_5

b; $C_6H_4OCH_3$ (P-)

c; $C_6H_4CH_3$ (P-)

d; C_6H_4Cl (P-)

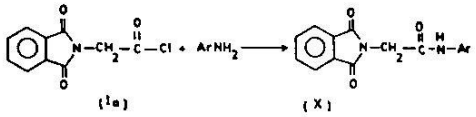
e; $C_6H_4CO_2H$ (o-)

f; $C_6H_4CO_2H$ (m-)

g; $C_6H_4CO_2H$ (P-)

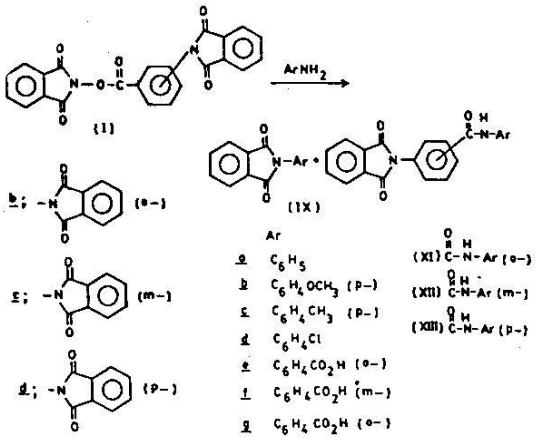
The structure of products (IXa-g) was established on the basis of their IR data and direct comparison (mmp) with authentic samples [6,8-11].

The structures of (Xa-g) were established by : (i) Their IR spectra showing νNH in the region (3300-3200 cm^{-1}), νC=O in the region (1680-1650 cm^{-1}) and doublet in the region (1790-1780 and 1720-1715 cm^{-1}) for coupling bands of cyclic imides [3,4]. (ii) ^{1}H-NMR spectra of (Xc) shows signals at δ 2.3 ppm and 4.5 ppm corresponding to CH_3- and CH_2- groups respectively, also δ 7.1 to 8 ppm corresponding to (8) aromatic protons, and of (Xf) shows singlet of δ 4.6 ppm corresponding to -CH_2 group and signals at δ 7.5 to 8.35 ppm corresponding to 8 aromatic protons. (iii) Authentically: by comparison with authentic samples prepared via the reaction of phthalylglycyl chloride with the corresponding aromatic amines and/or aminobenzoic acid.

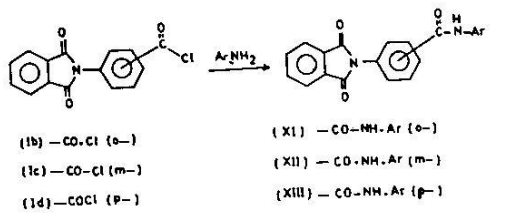


Similarly (IIb-d) reacted with the above mentioned aromatic amines and/or aminobenzoic acid to give the corresponding mixture of N-aryl-phthalimides (IXa-g) and N-phthalimido anilides (XI-XIII).

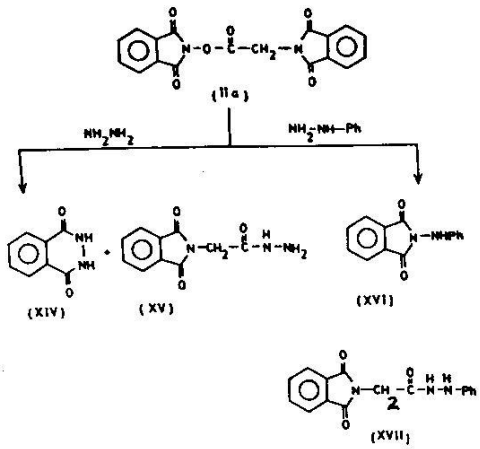
The structure of products (XI-XIII) were established by: (i) Their IR showed νNH in the region (3320-3250 cm^{-1}), νC=O of anilides in the region (1700-1650 cm^{-1}) and doublet in the region (1780-1770 and



1720-1710 cm^{-1}) for coupling bands of cyclic imides [3,4]. (ii) ^{1}H-NMR spectra of (XIIb) shows singlet at δ 3.75 corresponding to -OCH_3 attached to phenyl ring, and signals from δ 6.85 to δ 8.1 ppm corresponding to (12) aromatic protons. (iii) By direct comparison (mmp) with authentic specimens prepared via the reaction of o-, m-, and p-phthalimido benzoyl chlorides [7] with the above mentioned aromatic amines and/or aminobenzoic acids.



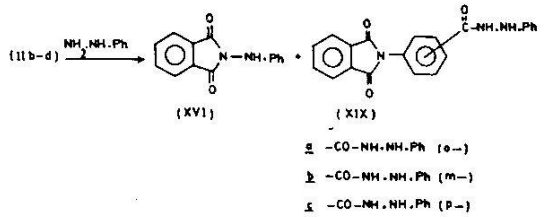
When (IIa) was allowed to react with hydrazine hydrate and/or phenylhydrazine, it gave the corresponding mixtures of phthalhydrazide (XIV), N-phthalimido acetic acid hydrazide (XVI) and N-anilinophthalimide (XVI), N-(phthalimido)-acetyl phenylhydrazine (XVII) respectively.



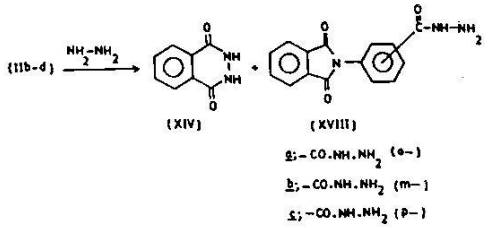
The structures of (XIV) and (XVI) were established on the basis of their IR data [6] and direct comparison (mmp) with authentic specimens [12,13].

Similarly the structures of (XV) and (XVII) were confirmed from their IR spectra which showed νC=O of hydrazide in the region (1680-1660 cm^{-1}), νNH at (3340-3220 cm^{-1}), νC=O of cyclic imide in the region (1780-1760 and 1720-1715 cm^{-1}) and direct comparison (mmp) with authentic specimens prepared via the reaction of phthalimido acetyl chloride with the corresponding hydrazines [1].

However (IIb-d) reacted with hydrazine hydrate to give N-(phthalimido) o-, m-, and p-benzoic acid hydrazide (XVIIIa-c) respectively.



Similarly (IIb-d) reacted with phenylhydrazine to give a mixture of N-anilinophthalimide (XVI) and the corresponding N-(phthalimido)benzoyl-phenylhydrazine (XXXa-c).



The structures of (XVIII) and (XIX) were confirmed by: (i) Their IR spectra which revealed the presence of νNH in the region (3300-3150 cm^{-1}), νC=O of hydrazide in the region (1680-1650 cm^{-1}) and coupling νC=O of cyclic imides in region (1790-1770 and 1720-1710 cm^{-1}) [3,4]. (ii) By direct comparison with authentic specimens prepared via the reaction of phthalimido-benzoyl chloride with the above mentioned hydrazines [7].

Experimental

All m.p.'s are not corrected, i.r. spectra were measured on a Unicam SP 1200 Spectrophotometer using KBr Wafter technique. The ^{1}H-NMR spectra were measured on EM-390 90 MHz NMR spectrometer. The mass spectra were measured on FINNIGAN MAT 8230 mass spectrometer at beam energy 70 ev, samples were introduced via direct insertion, ion source temperature were 220°C and mass resolution about 1000.

Synthesis of N-[phthalimido]acetoxy, o-, m-, and p-benzoyloxy phthalimides (IIa-d):

N-Hydroxyphthalimide (0.1 mole) was added to phthalimido acetyl chloride o-, m-, and p-phthalimido

Table-2: Physical data of N-[phthalimido]-acetoxy, o-, m-, and p-benzoyloxy phthalimides (IIa-d), (IIIa-c), (IV-VII), (VIIIa-c), (IXa-g), (X-XIII), (XIV-XVIII) and (XIX).

Compd No.	M.p. and m.m.p. °C	Yield (%)	Ref.	M.F.	Analysis %	Found	Calcd.
(IIa)	244-246[x]	55		$C_{18}H_{10}N_2O_6$	C	61.40	61.71
					H	2.45	2.85
					N	7.89	8.00
b	233-235[xx]	50		$C_{23}H_{12}N_2O_6$	C	66.83	66.99
					H	2.79	2.91
					N	6.78	6.80
c	251-253[xx]	59		$C_{23}H_{12}N_2O_6$	C	66.69	66.99
					H	2.82	2.91
					N	6.75	6.80
d	260-261[x]	64		$C_{23}H_{12}N_2O_6$	C	66.81	66.99
					H	2.80	2.91
					N	6.77	6.80
(IIIa)	160-162[xx]	50	6	$C_{14}H_9NO_2$			
b	162-164[xx]	67	6	$C_{15}H_{11}NO_2$			
c	145-147[xx]	63	6	$C_{15}H_{11}NO_3$			
(IVa)	164-166[x]	52		$C_{16}H_{11}NO_3$	C	72.30	72.45
					H	4.10	4.15
					N	5.21	5.28
b	182-184[x]	60		$C_{17}H_{13}NO_3$	C	73.10	73.12
					H	4.60	4.66
					N	4.95	5.02
c	150-152[x]	64		$C_{17}H_{13}NO_4$	C	69.09	69.15
					H	4.43	4.41
					N	4.67	4.75
(Va)	273-275[x]	70	7	$C_{21}H_{13}NO_3$			
b	266-268[x]	65	7	$C_{22}H_{15}NO_3$			
c	214-216[x]	72	7	$C_{22}H_{15}NO_4$			
(VIa)	163-165[xx]	60		$C_{21}H_{13}NO_3$	C	76.93	77.06
					H	3.79	3.98
					N	4.27	4.28
(VIb)	197-199[xx]	57		$C_{22}H_{15}NO_3$	C	77.38	77.42
					H	4.39	4.40
					N	4.10	4.11
c	180-182[xx]	65		$C_{22}H_{15}NO_4$	C	73.88	73.95
					H	4.18	4.20
					N	3.88	3.92
(VIIa)	179-181[x]	50	7	$C_{21}H_{13}NO_3$			
b	166-168[x]	67	7	$C_{22}H_{15}NO_3$			

Table-2 (Cont'd..)

Compd No.	M.p. and m.m.p. °C	Yield (%)	Ref.	M.F.		Analysis % Found	Calcd.
c	172-174[x]	63	7	$C_{22}H_{15}NO_4$			
(VIIIa)	198-200[x]	50	4	$C_{20}H_{15}NO_2$			
b	200-202[x]	52	4	$C_{22}H_{19}NO_2$			
c	267-269[x]	60	4	$C_{22}H_{19}NO_4$			
(IXa)	200-202[xx]	50	8	$C_{14}H_4NO_2$			
b	155-156[xx]	72	9	$C_{15}H_{11}NO_3$			
c	201-202[xx]	70	10	$C_{15}H_{11}NO_2$			
d	194-196[xx]	60	11	$C_{14}H_8NO_2Cl$			
e	215-217[xx]	45	6	$C_{15}H_9NO_4$			
f	272-274[xx]	60	6	$C_{15}H_9NO_4$			
g	279-280[xx]	72	6	$C_{15}H_9NO_4$			
(Xa)	220-227[xx]	60		$C_{16}H_{12}N_2O_3$	C	68.41	68.57
					H	4.30	4.29
					N	9.92	10.00
b	256-257[xx]	80		$C_{17}H_{14}N_2O_4$	C	65.71	65.81
					H	4.32	4.52
					N	8.99	9.03
c	259-261[xx]	75		$C_{17}H_{14}N_2O_3$	C	69.30	69.39
					H	4.70	4.76
					N	9.48	9.52
d	251-253[xx]	61		$C_{16}H_{11}N_2O_3Cl$	C	61.10	61.15
					H	3.48	3.50
					N	8.88	8.92
e	256-258[xx]	50		$C_{17}H_{12}N_2O_5$	C	62.90	62.96
					H	3.69	3.70
					N	8.60	8.64
(Xf)	283-285[xx]	61		$C_{17}H_{12}N_2O_5$	C	62.90	62.96
					H	3.78	3.70
					N	8.60	8.64
g	>300[ø]	70		$C_{17}H_{12}N_2O_5$	C	62.93	62.96
					H	3.67	3.70
					N	8.59	8.64
(XIa)	174-176[ó]	51	7	$C_{21}H_{14}N_2O_3$			
b	188-190[ó]	58	7	$C_{22}H_{16}N_2O_4$			
c	179-181[ø]	65	7	$C_{22}H_{16}N_2O_3$			
d	216-218[ø]	55	7	$C_{21}H_{13}N_2O_3Cl$			

Table-2 (Cont'd..)

Compd No.	M.p. and m.m.p. °C	Yield (%)	Ref.	M.F.		Analysis % Found	Calcd.
e	168-170[ø]	44	7	$C_{22}H_{14}N_2O_5$			
f	128-130[ø]	49	7	$C_{22}H_{14}N_2O_5$			
g	208-212[x]	53	7	$C_{22}H_{14}N_2O_5$			
(XIIa)	206-207[xx]	54		$C_{21}H_{14}N_2O_3$	C	73.58	73.68
					H	4.00	4.09
					N	8.10	8.19
b	199-201[xx]	60		$C_{22}H_{16}N_2O_4$	C	70.90	70.97
					H	4.28	4.30
					N	7.49	7.53
c	209-211[xx]	62		$C_{22}H_{16}N_2O_3$	C	74.07	74.16
					H	4.45	4.49
					N	7.82	7.87
d	217-219[xx]	61		$C_{21}H_{13}N_2O_3Cl$	C	67.00	67.02
					H	3.43	3.46
					N	7.41	7.45
e	261-263[xx]	50		$C_{22}H_{14}N_2O_5$	C	68.35	68.39
					H	3.60	3.63
					N	7.17	7.25
f	242-244[xx]	54		$C_{22}H_{14}N_2O_5$	C	68.34	68.39
					H	3.61	3.63
					N	7.14	7.25
g	300[xx]	53		$C_{22}H_{14}N_2O_5$	C	68.30	68.39
					C	3.58	3.63
					N	7.20	7.25
(XIIIa)	> 300[xx]	59	7	$C_{21}H_{14}N_2O_3$			
b	241-243[≠]	70	7	$C_{22}H_{16}N_2O_4$			
c	273-275[xx]	63	7	$C_{22}H_{16}N_2O_3$			
d	293-295[xx]	58	7	$C_{21}H_{13}N_2O_3Cl$			
e	246-248[x]	60	7	$C_{22}H_{14}N_2O_5$			
f	276-278[x]	58	7	$C_{22}H_{14}N_2O_5$			
g	287-289[ø]	62	7	$C_{22}H_{14}N_2O_5$			
(XIV)	> 320[xx]	50	12	$C_8H_6N_2O_2$			
(XV)	> 300[ø]	52	1	$C_{10}H_9N_3O_3$			
(XVI)	171-173[xx]	69	13	$C_{14}H_{10}N_2O_2$			

Table-2 (Cont'd..)

Compd No.	M.p. and m.m.p. °C	Yield (%)	Ref.	M.F.	Analysis % Found	Calcd.
(XVII)	138-140[xx]	65	1	$C_{16}H_{13}N_3O_3$		
(XVIIIa)	> 300[xx]	49	7	$C_{15}H_{11}N_3O_3$		
b	> 300[ø]	53	7	$C_{15}H_{11}N_3O_3$		
c	285-287[xx]	60	7	$C_{15}H_{11}N_3O_3$		
(XIXa)	198-200[xx]	58	7	$C_{21}H_{15}N_3O_3$		
b	216-218[ø]	50	7	$C_{21}H_{15}N_3O_3$		
c	248-250[xx]	63	7	$C_{21}H_{15}N_3O_3$		

x = benzene, xx = acetic acid, x = methanol, xx = ethanol,

ø = (benzene + methanol), ≠ = ethyl acetoacetate.

benzoyl chloride (0.13 mole) in 40 ml. of dry benzene and 2 drops of pyridine in dry round bottomed flask. The reaction mixture was heated under reflux for 3 hrs., then cooled and the solid products were filtered off and recrystallized from suitable solvent (cf. Table 2).

Action of anhyd. $AlCl_3$ (2 moles) on (IIa-d) in reactive aromatic substrate: Formation of 4-aryl-2,3,1-benzoxazone (IIIa-c) and (IV-VII):

Anhyd. $AlCl_3$ (2 moles) was added while stirring to a solution of (IIa-d) (0.1 mole) in dry aromatic substrate. The reaction mixture was refluxed for 1 hr. and the complex formed was decomposed with ice-cold dil. HCl. The solvent was steam distilled, the residual solid filtered, dissolved in hot ethanol, concentrated by evaporation and filtered off. The solid obtained was recrystallized from ethanol to give (IIIa-c, Table 2). The mother liquor was concentrated to give (IV-VII, Table 2).

Action of excess anhyd. $AlCl_3$ (6 moles) on (IIa-d) in reactive aromatic substrates: Formation of o-aroylanilides (VIIIa-c) and (IV-VII):

Anhyd. $AlCl_3$ (6 moles) was added while stirring to a solution of (IIa-d) (0.1 mole) in dry aromatic substrates. The reaction mixture was heated under reflux for 30 min. The complex formed was decomposed with ice-cold dil. HCl and the solvent was steam distilled, the residual solid was filtered off and recrystallized from methanol to give (IV-VII, Table 2). The mother liquor was concentrated to give (VIIIa-c, Table 2).

Reaction of (IIa-d) with aromatic amines and/or aminobenzoic acids: Formation of (IXa-g) and (X-XIII):

A mixture of (IIa-d) (0.1 mole) and aromatic amines or aminobenzoic acids (0.4 mole) in benzene (20 ml) was heated under reflux for 3 hr. and cooled. The solid products were filtered and recrystallized from ethanol

to give (IXa-g, Table 2) as white crystals. The mother liquor was concentrated and the solid products obtained were crystallized from ethanol to give (X-XIII, Table 2) as white crystals.

Reaction of (Ia-d) with aromatic amines and/or aminobenzoic acids: Formation of (X-XIII):

A mixture of (Ia-d) (0.1 mole) and aromatic amines or aminobenzoic acids in dry benzene was heated under reflux for 20 min. and then cooled. The solid products were filtered and crystallized from ethanol to give (X-XIII, Table 2).

Reaction of (IIa-d) with hydrazine hydrate: Formation of (XIV, XV) and (XVIII):

A mixture of (IIa-d) (0.1 mole) and hydrazine hydrate (0.3 mole) in benzene was refluxed for 3 hr. and cooled. The solid product obtained was filtered and crystallized from ethanol to give (XIV, Table 3) as white crystal. The mother liquor was concentrated and crystallized from suitable solvent to give (XV and XVIII, Table 2).

Reaction of (IIa-d) with phenylhydrazine: Formation of (XVI, XVII) and (XIX):

A mixture of (IIa-d) (0.1 mole) and phenylhydrazine (0.3 mole) in benzene was refluxed for 3 hr. and cooled. The solid product obtained was filtered and crystallized from ethanol to give (XVI, Table 3) as yellow crystals. The mother liquor was concentrated and the solid products obtained were crystallized from suitable solvent to give (XVII and XIX, Table 2).

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