Alkylation of Amines with β-Aroylacrylic Acids and some Studies on the Alkylating Products

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Summary : β-Aroylacrylic acids (**1a-d**) react with primary amines and secondary amines to give the corresponding α-alkylamino-β-aroyl-propionic acids (**2a-r**) and (**3 a-h**). Treatment of (**2c**) and/or (**2e**) with acetic anhydride gave the butenolide (**4**) and the ketone (**5**). Reaction of (**4**) with phenylhydrazine gave the phenylhydrazone (**6**). Reaction of (**2e**) with hydrazine and/or phenylhydrazine gave the pyridazinone derivatives (**7a** and **b**).

β-Aroylacrylic acids were found to possess antihypertensive and antidepressant activities and some derivatives are used in formulations of medicaments [1].

Recently [2-5] it has been reported that β-aroylacrylic acids reacted with nitrogen nucleophiles like amines to give the corresponding propionic acid derivatives. In this study, treatment of β-aroylacrylic acids (**1a-d**) in benzene with primary amines, namely, n-butylamine, benzylamine, aniline, p-toluidine, m-chloroaniline, 5-chloro-2-methyaniline and 2-aminopyridine gave corresponding α-akyl-or arylamino-β-aroylpropionic acids (**2a-r**) respectively.

The assigned structure for the propionic acid derivatives (2) was inferred from the following:

i) Correct analytical data.

ii) The IR spectra of (2) showed absorption bands at 1730-1695 cm^{-1} (ν_{C-H}) and a broad band in the region 3420- 3200 cm^{-1} (ν_{NH} and /or ν_{OH}).

iii) The NMR spectrum of (**2a**) showed signals at δ 1.3 ppm (m, 7H of $CH_3CH_2CH_2$-), δ 2.5 ppm (m, 2H of CH_2-NH), δ 2.7-2.8 ppm (m, 2H of $COCH_2CH$-), δ 4.5-4.9 ppm (m, 1H, of methine proton) and at δ 6.8-8.3 ppm (m, 9H of aromatic protons).

The NMR spectrum of (**2c**) showed signals at δ 2.45- 2.65 ppm (q, 2H of -$CH_2C_6H_5$), δ 3.95-4.1

(1)

a, Ar = $C_6H_5O.C_6H_4$
b, Ar = 3,4-$Cl_2C_6H_3$
c, Ar = $C_6H_3(CH_3)Cl$ (5,2)
d, Ar = $C_6H_3(CH_3)Cl$ (3,4)

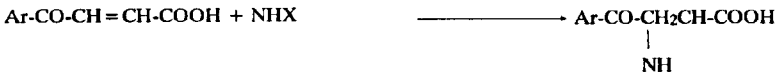
(2)

a,	Ar = $C_6H_5O.C_6H_4$	X = $CH_3(CH_2)_{3-n}$
b,	Ar = 3,4-$Cl_2C_6H_3$	X = $CH_3(CH_2)_{3-n}$
c,	Ar = $C_6H_5O.C_6H_4$	X = $CH_2C_6H_5$
d,	Ar = 3,4-$Cl_2C_6H_3$	X = $CH_2C_6H_5$
e,	Ar = $C_6H_3(CH_3)$ Cl(5,2)	X = $CH_2C_6H_5$
f,	Ar = $C_6H_3(CH_3)Cl$ (3,4)	X = $CH_2C_6H_5$
g,	Ar = $C_6H_5 = O.C_6H_4$	X = Ph
h,	Ar = 3,4-$Cl_2C_6H_3$	X = Ph
i,	Ar = $C_6H_5O.C_6H_4$	X = $C_6H_4CH_3$-p
j,	Ar = 3,4-$Cl_2C_6H_3$	X = $C_6H_4CH_3$-p
k,	Ar = $C_6H_3(CH_3)Cl(5,2)$	X = $C_6H_4CH_3$-p
l,	Ar = $C_6H_5O.C_6H_4$	X = C_6H_4Cl-m
m,	Ar = 3,4-$Cl_2C_6H_3$	X = C_6H_4Cl-m
n,	Ar = $C_6H_5O.C_6H_4$	X = $C_6H_3(CH_3)Cl$ (5,2)
o,	Ar = 3,4-$Cl_2C_6H_3$	X = $C_6H_3(CH_3)$ Cl (5,2)
p,	Ar = $C_6H_3(CH_3)$ Cl (5,2)	X = $C_6H_3(CH_3)$ Cl (5,2)
q,	Ar = $C_6H_3O.C_6H_4$	X = C_5H_4N-2
r,	Ar = C_6H_3 (CH_3) Cl (5,2)	X = C_5H_4N-2

ppm (q, 2H of -CH_2CH-), δ 5.35-5.7 ppm (m, 1H of-CH-) and at δ 6.8-8.3 ppm (m, 9H of aromatic protons).

The mechanism of the reaction possibly involves the electrophilic attack of the amine to the positively charged α-carbon of β-aroylacrylic acid giving rise to a positively charged intermediate followed by re-arrangement to give the product (II).

Similarly, the reaction of β-aroylacrylic acid (**1a- c**) in benzene with secondary amines, namely piperidine, dimethylamine, diethylamine, morpholine and piperazine gave the corresponding α-alkylamino-β-aroylpropionic acids (**3a-h**) respectively.



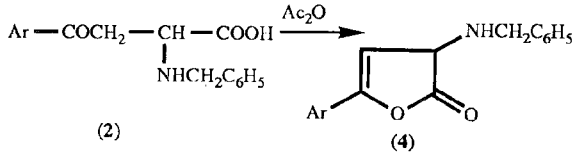
(1) (3)

a, Ar = C_6H_5-O-C_6H_4
b, Ar = 3,4-Cl_2-C_6H_3
c, Ar = $C_6H_3(CH_3)Cl$(5,2)

a,	Ar = C_6H_5-O-C_6H_4,	X = C_5H_{10}
b,	Ar = 3,4-$Cl_2C_6H_3$,	X = $(CH_3)_2$
c,	Ar = 3,4-$Cl_2C_6H_3$,	X = $(C_2H_5)_2$
d,	Ar = 3,4-$Cl_2C_6H_3$,	X = C_5H_{10}
e,	Ar = $C_6H_3(CH_3)$(Cl(5,2),	X = C_5H_{10}
f,	Ar = C_6H_5-O-C_6H_4,	X = C_4H_8O
g,	Ar = 3,4-$Cl_2C_6H_3$,	X = C_4H_8O
h,	Ar = C_6H_5O-C_6H_4,	X = C_4H_8NH

The structure of the acids (**3**) was proved by analysis and IR spectra which revealed the presence of $\nu_{C=O}$ (carboxylic) in the region 1700-1650 cm^{-1}, ν_{C-N} in the region 1300-1250 cm^{-1}, ν_{C-H} in the region 3000-2740 cm^{-1} and ν_{OH} in the region 3530-3410 cm^{-1}. The IR spectrum of (**3h**) revealed a stretching frequency at 3440 cm^{-1} attributed for ν_{NH}.

This work also investigated the action of acetic anhydride on α-benzylamino-β-(P-phenoxy)-benzoylpropionic acid (2c) and α-benzyl-amino- β-(2-methyl-5-chloro)-benzoylo-priopionic acid (2e). Thus, treatment of (2c) and/or (2e) with warmed acetic anhydride yielded the corresponding α-(substituted phenyl)-γ-(benzylamino)-Δ-β,γ-butenolides (4 a and b) as well as the ketones (5 a and b) respectively.



(2) (4)

c, Ar = C_6H_5 - O- C_6H_4
e, Ar = $C_6H_3(CH_3)Cl_{(5,2)}$

+

Ar - $COCH_2CH_2NHCH_2C_6H_5$
(5)

a, Ar = C_6H_5 - O - C_6H_4
b, Ar = $C_6H_3(CH_3)Cl$(5,2)

The structure (**4**) and (**5**) were established from:

i) Correct analytical data:

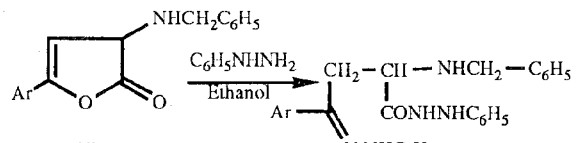
ii) Spectroscopically:

a- IR spectra of (**4**) showed bands at 1730 cm^{-1}, 1605-1590 cm^{-1}, 1175 cm^{-1} and at 3450 cm^{-1} attributed to $\nu_{C=O}$ of β,γ-unsaturated-γ-lactone, ν-lactone, $\nu_{C=C}$, ν_{C-O} and ν_{NH} respectively.

b- The IR spectra of (**5**) showed bands at 1670-1660 cm^{-1} and 3465- 3460 cm^{-1} due to $\nu_{C=O}$ aroyl and ν_{NH}.

c- The NMR spectrum of (**4a**) showed signals at δ 3.1-3.4 ppm (d, 2H of -CH_2-C_6H_5) and at δ 6.9-7.67 ppm (m, 14H of aromatic protons).

Structure of (**4 a and b**) was further supported by its treatment with phenylhydrazine in boiling ethanol to yield α-(phenylhydrazone)-α-(benzylami-no)-β-(aroylphenylhydrazide)-propionic acids (**6 a and b**).



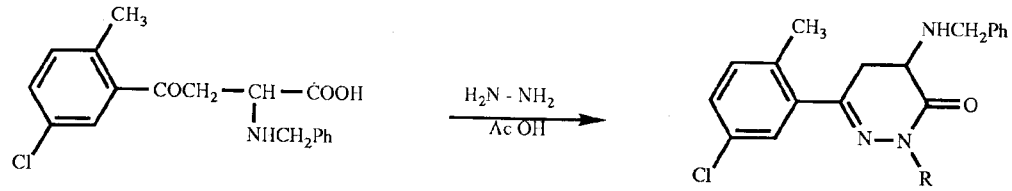
(4) (6)

a, Ar = C_6H_5-O-C_6H_4
b, Ar = $C_6H_3(CH_3)$ Cl(5,2)

The structure of (**6**) was established from the correct analytical data and IR spectra which revealed the absence of $\nu_{C=O}$ of aroyl and the presence of $\nu_{C=O}$ of amide at 1640 cm^{-1} and ν_{NH} at 3480-3410 cm^{-1}.

The mechanism of the reaction possibly involves ring fission of (4) by the nitrogen nucleophile leading to the formation of an intermediate which was attacked by another molecule of phenylhydrazine forming via condensation reaction the stable amide (6).

In addition, the reaction of the acid (2) with hydrazine [6,7] was investigated. Thus, α-benzylamino- β-(5-chloro-2-methyl-benzoyl)-propionic acid (2e) reacted with hydrazine hydrate and/or phenylhydrazine in acetic acid afforded the pyridazin-3-one derivatives (7 a and b) respectively.



(2e) (7)

a, R = H
b, R = C_6H_5

The IR spectrum of (7) showed bands attributed for $\nu_{C=O}$ at 1670 cm^{-1}, $\nu_{C=N}$ at 1590 cm^{-1} and ν_{NH} at 3280 cm^{-1}.

The NMR spectrum of (7b) showed signals at δ 2.55 ppm (s, 3H of Ar-CH_3), δ 3.5 ppm (m, 2H of-CH_2-CH-), δ 5.2 ppm (m, 3H of-CH_2-C_6H_5 and -CH_2-CH-), δ 7.8 ppm (m, 13H of aromatic protons) and at δ 9.25 ppm (broad signal, 1H,-NH-CH_2).

The formation of the pyridazinone (7) could be possibly taken place by the nucleophilic attack to the aroyl carbonyl carbon followed by ring closure with loss of water.

Experimental

All melting points reported in Table 1 are uncorrected. The infrared absorption spectra were determined with a Unicam SP 1200 spectrophotometer using KBr wafer technique. The NMR spectra were determined by a Varian analytical instrument division chart S-60T using TMS as an internal standard and DMSO as solvent. The analytical and physical data of all products are described in Table 1.

Reaction of β-aroylacrylic acids (1 a-d) with primary amines; formation of α-substituted-amino-β-aroylpropionic acids (2 a-r)

A solution of (1a-d) (0.01 mole) in benzene (100 ml) and primary aliphatic and aromatic amines, namely n-butylamine, benzylamine, aniline, p-toluidine, m-chloroaniline, 5-chloro-2-methylaniline and 2-aminopyridine (0.01 mole) was standing at room temperature for 30 minutes. The solid obtained was crystallised from the suitable solvent to give (2a-r).

Reaction of β-aroylacrylic acids (1a-c) with secondary amines; formation of (3 a-h)

A solution of (1a-c) (0.01 mole) in benzene (100 ml) and secondary amines, namely piperidine, dimethylamine, diethylamine, morpholine and piperazine (0.01 mole) was standing at room temperature for 30 minutes. The solid obtained was crystallised from the appropriate solvent to give (3a-h).

Action of acetic anhydride on (2c) and (2e); Formation of the butenolide (4 a and b) and the ketone (Va and b).

A mixture of (2 c) and/or (2e) (0.01 mole) and a freshly fused sodium acetate (0.05 mole) in acetic anhydride (20 ml) was warmed on a water bath for 30 minutes. The solid product separated after cooling was crystallised from benzene to give (4a and b) and (5a and b).

Reaction of the butenolide (4a and b) with a phenylhydrazine; Formation of (6 a and b)

A mixture of (6 a and b) (0.01 mole) and phenylhydrazine (0.01 mole) in ethanol (20 ml) was

Table 1: Characterisation of the organic compounds (1-7)

Com-. poud	m.p.°C colour	Solvent yield %	Mol.formula Mol.wt.	Analysis Calcd.	Found
2a	179	E	$C_{20}H_{23}NO_4$	C, 70.38	70.72
	White	80	341	H, 6.74	6.44
				N, 4.10	4.53
2b	144	E	$C_{14}H_{17}Cl_2NO_3$	C, 52.83	52.64
	White	70	318	H, 5.34	5.68
				N, 4.40	4.83
				Cl, 22.32	22.70
2c	168	A	$C_{23}H_{21}NO_4$	C, 73.60	73.32
	White	80	375	H, 5.60	5.41
				N, 3.73	3.43
2d	120	E	$C_{17}H_{15}Cl_2NO_3$	C, 57.95	58.64
	P.yellow	85	352	H, 4.26	4.50
				N, 3.97	4.33
				Cl, 20.17	20.56
2e	157	E	$C_{18}H_{18}ClNO_3$	C, 65.15	65.50
				H, 5.42	5.74
				N, 4.22	4.52
	White	75	331.5	Cl, 10.70	10.33
2f	137	T	$C_{18}H_{18}ClNO_3$	C, 65.15	65.54
				H, 5.42	5.82
				N, 4.22	4.53
	White	65	331.5	Cl, 10.70	10.46
2g	124	T	$C_{22}H_{19}NO_4$	C, 73.13	73.45
				H, 5.26	5.52
	White	70	361	N, 3.87	3.43
2h	125	E	$C_{16}H_{13}Cl_2NO_3$	C, 56.80	56.64
				H, 3.84	3.61
	P.brown	40	338	Cl, 21.00	21.62
				N, 4.14	4.30
2i	116	E	$C_{23}H_{21}NO_4$	C, 73.60	73.33
				H, 5.60	5.30
	P.brown	70	375	N, 3.73	3.42
2j	160	E	$C_{17}H_{15}Cl_2NO_3$	C, 57.95	58.36
				H, 4.26	4.69
				N, 3.97	4.33
	P.brown	30	352	Cl, 20.17	20.72
2k	189	E	$C_{18}H_{18}ClNO_3$	C, 65.15	65.60
	P.yellow	30	331.5	H, 5.42	5.77
				N, 4.22	4.62
				Cl, 10.70	10.32
2l	146	T	$C_{22}H_{18}ClNO_4$	C, 66.75	66.43
	P.brown	50	395.5	H, 4.55	4.20
				N, 3.53	3.13
				Cl, 8.97	8.46
2m	115	E	$C_{16}H_{12}Cl_3NO_3$	C, 57.95	58.24
				H, 4.26	4.65
				N, 3.97	4.30
	Yellow	30	372.5	Cl, 20.17	20.62
2n	138	E	$C_{23}H_{20}ClNO_4$	C 67.39	67.68
	Yellow	50	409.5	H, 4.88	4.60
				N, 3.41	3.13
				Cl, 8.66	8.15
2o	275	A	$C_{17}H_{14}Cl_3NO_3$	C, 52.78	52.36
	P.grey	50	386.5	H, 3.62	3.23
				N, 3.62	3.38
				Cl, 27.55	27.14
2p	205	E	$C_{18}H_{17}Cl_2NO_3$	C, 59.01	59.62
				H, 4.64	4.24
	Yellowish			N, 3.82	3.43
	green	40	366	Cl, 19.39	19.96
2q	155	E	$C_{21}H_{18}N_2O_3$	C, 69.13	69.43
				H, 4.97	4.68
	Yellow	40	362	N, 7.73	7.18

Table 1: (contd.)

Com-. poud	m.p.°C colour	Solvent yield %	Mol.formula Mol.wt.	Analysis Calcd.	Found
2r	198	E	$C_{16}H_{15}ClN_2O_3$	C, 60.28	60.63
				H, 4.70	4.38
				N, 8.79	8.42
	P.pink	50	318.5	Cl, 11.14	11.60
3a	135	E	$C_{21}H_{23}NO_4$	C, 71.38	71.61
				H, 6.51	6.32
	White	70	353	N, 3.96	3.79
3b	120	E	$C_{12}H_{13}Cl_2NO_3$	C, 49.65	49.20
				H, 4.48	4.85
	Yellow	30	290	N, 4.82	4.48
3c	138	T	$C_{14}H_{17}Cl_2NO_3$	C, 52.83	52.54
				H, 5.34	5.62
	Yellow	30	318	N, 4.40	4.82
3d	152	E	$C_{15}H_{17}Cl_2NO_3$	C, 54.54	54.88
				H, 5.15	5.30
	White	80	330	N, 4.24	4.60
3e	160	E	$C_{16}H_{20}ClNO_3$	C, 62.03	62.31
				H, 6.64	6.81
	White	50	309.5	N, 4.52	4.89
3f	140	140	E $C_{20}H_{21}NO_5$	C, 67.60	67.98
				H, 5.91	5.63
	P.yellow	50	355	N, 3.94	3.66
3g	151	E	$C_{14}H_{15}Cl_2NO_4$	C, 50.60	50.36
				H, 4.51	4.69
	White	30	332	N, 4.21	4.00
3h	205	A	$C_{20}H_{22}N_2O_2$	C, 67.79	67.48
				H, 6.21	6.60
	P.yellow	60	354	N, 7.90	7.69
4a	115	B	$C_{23}H_{19}NO_3$	C, 77.31	77.69
				H, 5.32	5.64
	Yellow	30	357	N, 3.92	3.76
4b	120	B	$C_{18}H_{16}ClNO_2$	C, 68.89	68.55
				H, 5.10	5.45
	Yellow	30	313.5	N, 4.46	4.61
5a	125	B	$C_{22}H_{21}NO_2$	C, 79.75	79.49
				H, 6.34	6.13
	White	40	331	N, 4.22	4.59
5b	124	B	$C_{17}H_{18}ClNO_3$	C, 70.95	70.69
				H, 6.26	6.48
	White	50	287.5	N, 4.86	4.61
6a	95	B	$C_{35}H_{33}N_5O_2$	C, 75.67	75.50
				H, 5.94	5.63
	P.brown	40	555	N, 12.61	12.40
6b	105	T	$C_{30}H_{30}ClN_5O$	C, 70.38	70.00
				H, 5.86	6.51
	P.brown	45	511.5	N, 13.60	13.89
7a	88	B	$C_{18}H_{18}ClN_3O$	C, 65.95	65.69
				H, 5.49	5.73
	P.brown	60	327.5	N, 12.82	12.52
7b	198	E	$C_{24}H_{22}ClN_3O$	C, 71.37	71.01
				H, 5.45	5.71
	Brown	75	403.5	N, 10.40	10.70

Where A = Acetic acid, B = Benzene, T = Toluene and E = Ethanol.

refluxed for 3 hrs. The solid product separated after concentration and cooling was crystallised from the proper solvent to give **(6 a and b)**

Reaction of the acid (2e) (0.01 mole), hydrazine and/or phenylhydrazine (0.01 mole) in

glacial acetic acid was refluxed for 3 hrs. The reaction mixture was left at room temperature over night. The solid product separated after concentration and cooling was crystallised from the suitable solvent to give (**7 a and b**).

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