Epoxidation and Michael Reaction of β-3,4-Dimethylbenzoylacrylic Acid

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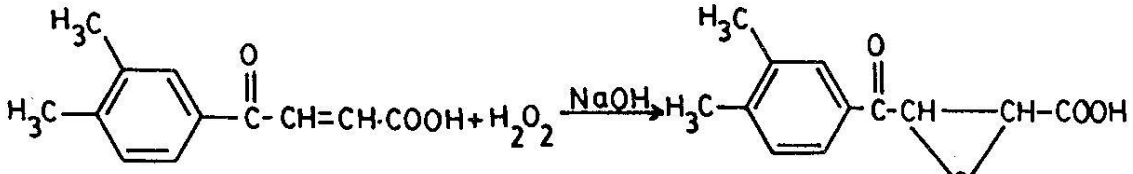
Summary: -3,4-Dimethylbenzoylacrylic acid (I) reacts with hydrogen peroxide to give the corresponding epoxide (II) and with acetyl acetone under Michael conditions to give the corresponding Michael addition product (VII) or cyclic product (VIII). The action of hydrazines, amines, hydroxylamine hydrochloride, urea and thioureas on these products has been described.

While continuing our studies on β-aroylacrylic acids[1-5], we have investigated the reaction of β-3,4-dimethylbenzoylacrylic acid with hydrogen peroxide and with acetylacetone under Michael condition with a view to synthesizing hitherto unknown derivatives of these compounds.

Thus, treatment of methanolic solution of β-3,4-dimethyl-benzoylacrylic acid (I) with hydrogen peroxide in NaOH solution gave the corresponding α β-epoxy- β-(3,4-dimethylbenzoyl)-acrylic acid (II).



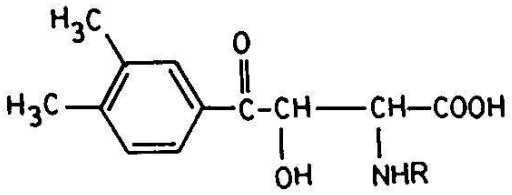
(I) (II)

The NMR spectrum of the unknown epoxide(II)in DMSO shows signals at δ 7.20-8.10 ppm (3H, m, aromatic protons), δ 3.25, 3.30 (2H, two d, -CH-CH- J = 4.5 Hz) at δ 2.45 (6H, s, two CH_3).

The epoxide ring is easily opened at α-carbon on treatment with amines due to both strong electron withdrawing action of the carbonyl group and steric factor. Consequently αcarbon atom accepts the nucleophiles more readily than the β-carbon. Thus, reaction of (II) with benzylamine or p-toluidine in boiling ethanol led to the formation of α-arylamino-β-hydroxy- β-(3,4-dimethyl-benzoyl)-propionic acid derivatives (IIIa and b) respectively.

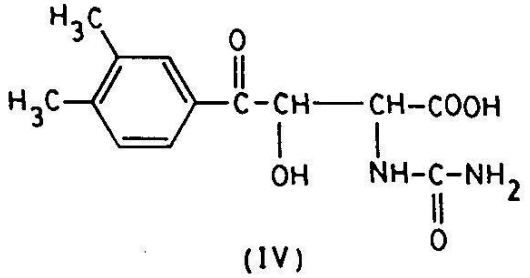
The N.M.R. spectrum of (IIIa) in $CDCl_3$ shows signals at δ 6.95-7.50 (8H, m, aromatic protons), at δ 4.10, δ 3.90 ppm (2H, d, -CH-CH-. J = 6.3 Hz) δ 3.70 ppm(2H, d, -NH-CH_2-, J = 5.6 Hz) and at δ 2.15 ppm (6H, s, two CH_3).

Similarly boiling a solution of (II) in ethanol with urea led to fission of the epoxide ring with the formation of α-aryl-β-hydroxy-β-3,4-dimethyl-propionic acid (IV).



(III)

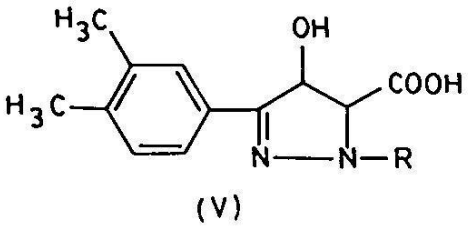
a, R = $CH_2C_6H_5$ b, R = $C_6H_4CH_3$ (p)



(IV)

The N.M.R. spectrum of (IV) shows signals at δ 8.50 (2H, s, NH_2), 8.10 (1H, s, NH), δ 7.20-7.75 (3H, m, aromatic protons), δ 3.95, δ 3.70 (2H, d, -CH-CH-, J = 6.4 Hz) and δ 2.40, δ 2.0 (6H, s, two CH_3 groups).

On the other hand, condensation of (II) with hydrazine hydrate or phenylhydrazine in boiling ethanol gave rise to 1-alkyl-β-(3,4-dimethyl-phenyl)-4-hydroxy-carboxypyrazolines (Va and b) respectively.

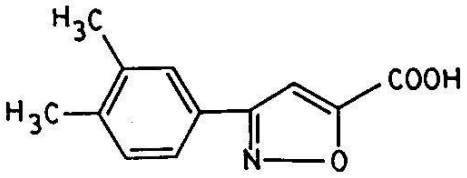


(V)

a, R = H b, R = C_6H_5

The N.M.R. spectrum of (Vb) shows signals at δ 6.90-8.05 (8H, m, aromatic protons), δ 4.25, δ 4.15 (2H, d, -CH-CH, J = 6.4 Hz), δ 8.50 (1H, OH) and δ 2.35, δ 2.25 (6H, s, two CH_3).

Reaction of (II) with hydroxylamine hydrochloride in pyridine led to formation of the isoxazole derivative (VI).

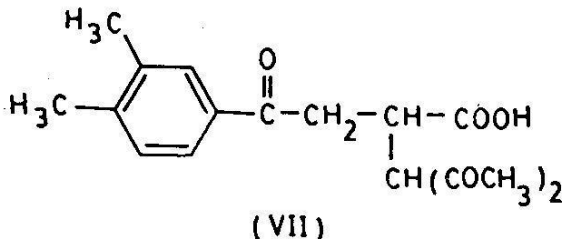


(VI)

The N.M.R. spectrum of (VI) in $CDCl_3$ shows signals at δ 7.10-7.95 (3H, m, aromatic protons), δ 4.20 ppm (1H, s, -CH=C-H, COOH) and at δ 2.50-2.60 (6H, s, two CH_3 groups).

Michael condensation of acetylacetone with β-3, 4-dimethyl-benzoylacrylic acid (I) produced the corresponding open chain addition product or cyclic derivative depending on the reaction conditions.

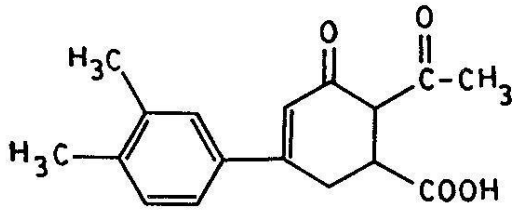
Acetylacetone readily added to (I) in the presence of sodium methoxide, at room temperature to give an open chain addition product [6] (VIII).



(VII)

The N.M.R. spectrum of (VII) shows signals at δ 7.15-7.80 (3H, m, aromatic protons), δ 3.80 (1H, d, $-C\underline{H}(COCH_3)_2$), δ 3.40 (1H, 2d, $C\underline{H}.COOCH$, part of ABx system, J_{AX} =12 Hz, J_{BX} = 12 Hz) [7], δ 3.15, 2.90, 2.60, 2.25 (12 H,s, four CH_3 groups) and at δ 2.05 (2H, m, $C\underline{H}_2$, part of ABx system, J_{AB} = 18.4 Hz).

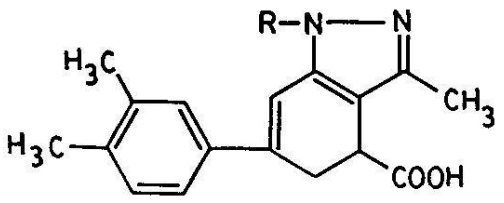
Ring closure of(VII)was accomplished by fusion with sodium methoxide at 160-170°C for 3 hrs to give β-(3,4-dimethylphenyl)-6-acetyl-3-oxo-cyclohexene-1-carboxylic acid (VIII) which can be obtained directly via fusion of the acid (I) with acetylacetone in sodium methoxide at 160-170° for 5 hours.



(VIII)

The N.M.R. spectrum of (VIII)shows signals at δ 7.40-6.65 (3H, m, aromatic protons), δ 6.40 (1H, d, cyclic $-C\underline{H}-\overset{O}{\overset{\|}{C}}-CH_3$, J = 10 Hz), δ 3.80 (1H, two d, cyclic -CH-COOH, part of ABx system, J_{Ax} = 12 Hz, J_{Bx} = 12Hz), δ 3.35(2H, m, cyclic $-C\underline{H}_2-$, part of ABx, J_{AB} = 18 Hz), δ 2.50 (3H, s, $-\overset{O}{\overset{\|}{C}}-C\underline{H}_3$) and δ 2.20,δ2.05 (6H, s, two CH_3).

Condensation of (VIII) with hydrazine hydrate in boiling glacial acetic acid or n-butyric acid gave the corresponding 1-acyl-4,5-dihydro-3-methyl-6-(3,4-dimethylphenyl)-1H-indazole-4-carboxylic acids (IXa and b) respectively.



(IX)

a, $R = COCH_3$

b, $R = COCH_2CH_2CH_3$

c, $R = C_6H_5$

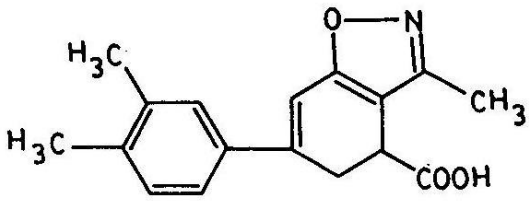
The N.M.R. spectrum of (IXb) shows signals at δ 7.10-7.20 (3H, m, aromatic protons), δ 6.85 (1H, two d, -CH-, part of ABx system J_{AX} = 12 Hz, J_{BX} = 12Hz), δ 2.65 (2H, m, $CH_3-CH_2-C\underline{H}_2-\overset{O}{\overset{\|}{C}}-$) δ 2.40, 2.30, 2.20 (9H, s, three $C\underline{H}_3$ groups), δ 2.75 (2H, m, cyclic $-C\underline{H}_2-$, part of ABx system, J_{AB} = 18.2 Hz) and at δ 1.50-1.90 (5H,q,t,$C\underline{H}_3-C\underline{H}_2$).

Similarly, condensation of (VIII) with phenylhydrazine in boiling ethanol gave the corresponding indazole derivative (IXc).

The N.M.R. spectrum of (IXc) shows signals at δ 6.85,δ7.35 (8H,m,aromatic protons), δ 6.50 (1H, two d, cyclic, -CH-C, part of ABX system, J_{AX} = 6.4, J_{BX} = 6.4),δ 3.80 (2H, m, cyclic $-C\underline{H}_2-$ part of ABX system J_{AB} = 18.2 Hz), δ 3.20 (3H, s, $C\underline{H}_3-C=$) and at δ2.20,2.30 (6H, s, two $C\underline{H}_3$ groups).

Treatment of (VIII) with hydroxylamine hydrochloride in the presence of sodium acetate led to the formation

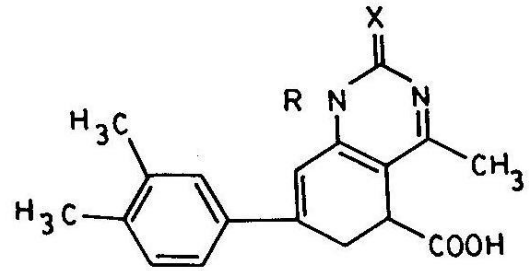
of the corresponding benzisoxazole derivative (X).



(X)

The N.MR. spectrum of (X) shows signals at δ6.90-7.35 (3H, m, aromatic protons) δ 6.60 (1H, two d, cyclic -CH-COOH, part of ABx system J_{AX} = 6.4 Hz, J_{BX} = 6.4 Hz), δ 3.65 (1H, s, -CH-C=), δ 2.70 (2H, m, part of ABx system, J_{AB} = 18 Hz) and δ2.45, δ2.20, δ2.10(9H, s, three CH_3 groups).

Reaction of (VIII) with urea, thiourea or benzylthiourea in boiling absolute ethanol gave the corresponding oxo- and thioxoquinazoline derivatives (XIa-c) respectively.



(XI)

	R	X
a,	H	O
b,	H	S
c,	$CH_2C_6H_5$	S
d,	$COCH_3$	O

Condensation of (VIII) with urea in boiling glacial acetic acid led to formation of the corresponding N-acetyloxo-quinazoline derivative (XId) which can be obtained alternatively via boiling of (XIa) with glacial acetic acid for 3 hours.

Experimental

The infrared spectra were taken on a Perkin-Elmer infrared spectrophotometer, Model 621 and given in Table 2. The N.M.R. spectra were determined with a Varian Model 390 Spectrophotometer.

All melting points were uncorrected.

Epoxidation of (I): Formation of (II)

A solution of (I) (0.01 mole) in acetone (20 ml) and methanol (10 ml) was treated with 8% aqueous NaOH (6 ml) followed by hydrogen peroxide (30%, 5 ml). The solution was shaken and brought to boiling point during one hour and then left overnight at room temperature, water was then added and the solution acidified with dilute hydrochloric acid.

The solid product was filtered off and crystallized from a mixture of pet. ether (b;p. 60-80°) and benzene to give the corresponding acrylic acid epoxide (II) as colourless crystals (cf. Table 1).

Reaction of (II) with amines: Formation of (IIIa) and (b)

A mixture of (II) (0.01 mole), benzylamine or p-toluidine (0.01 mole) and ethanol (20 ml) was refluxed for 4 hours. The solid product obtained after evaporation of most of ethanol and cooling were crystallized from ethanol to give the corresponding

The N.M.R. spectra of (IXa-c) in $CDCl_3$ show the following signals as represented in the table.

Compound	δ-value	J-values (Hz)	Group
XIa	6.95-7.30 (m)		8H aromatic protons
	6.35 (two d)	Ax=6.2	1H-CH-COOH
		Bx=6.2	(Part of ABx system)
	3.15(s)		1H cyclic -C-CH=C
	2.95(m)	AB=18	2H cyclic $-CH_2$
			(Part of ABx system)
	7.75(s)		9H three CH_3 group
	2.30(s)		
XIb	6.90-7.20(m)		3H aromatic protons
	6.30 (two d)	Ax=6.2	1H-CH-COOH
		Bx=6.2	(Part of ABx system)
	3.00(s)		1H cyclic -C-CH-C
	2.65(m)	AB=18	2H cyclic $-CH_2-$
			(Part of ABx system)
	2.20(s)		9H three CH_3 groups
	8.60(s)	1H-NH-	
XIc	6.75-7.00(m)		3H aromatic protons
	6.05(two d)	Ax=6.0	1H cyclic -CH-COOH
		Bx=6.0	(Part of ABx system)
	3.45(s)		1H cyclic -C-CH-C
	2.65(m)	AB=18	2H cyclic $-CH_2-$ group
			(Part of ABx system)
	3.20(s)		2H-CH_2-C_6H_5
	2.15-2.30		9H three CH_3 groups.

amine adducts (IIIa) and (b) respectively as colourless crystals (cf. Table 1).

Reaction of (II) and (VIII) with urea and thioureas: Formation of (IV) and (XIa-d)

A mixture of (II) or (VIII) (0.01 mole), urea, thiourea or benzylthiourea (0.02 mole) and ethanol (15 ml) was treated with a few drops of glacial acetic acid or in 15 ml glacial acetic acid and refluxed for 8 hours. The solid product formed after evaporation of most of the solvent and cooling was crystallized from proper solvent to give the corresponding products (IV) and (XIa-d) respectively (cf. Table 1).

Reaction of (II) and (VIII) with hydrazines: Formation of (Va and b) and (IXa-c)

A mixture of (II) or (VIII) (0.01 mole), hydrazine hydrate or phenylhydrazine (0.01 mole) and ethanol or glacial acetic acid or n-butyric acid (15 ml), was refluxed for 6 hours.

Table-1: The Physical data of new compounds

Compd	M.p. (°C)	Solvent*	Yield %	Formula	Found C	Found H	Found N	Required C	Required H	Required N
(II)	195	(P/B)	65	$C_{11}H_{12}O_4$	63.24	5.58	-	63.46	5.76	-
(IIIa)	212	(E)	70	$C_{19}H_{21}O_4N$	69.45	6.30	4.16	69.72	6.42	4.28
(IIIb)	245	(E)	50	$C_{19}H_{21}O_4N$	69.52	6.13	3.96	69.72	6.42	4.28
(IV)	182	(E)	60	$C_{13}H_{16}O_5N_2$	55.46	5.18	9.54	55.71	5.71	10.00
(Va)	290	(E)	50	$C_{12}H_{14}O_3N_2$	60.86	5.72	11.82	61.53	3.98	11.96
(Vb)	240	(E)	60	$C_{18}H_{19}O_3N_2$	69.15	6.22	8.87	69.45	6.10	9.00
(VI)	167	(E)	50	$C_{12}H_{11}O_3N$	66.22	4.87	6.28	66.35	5.06	6.45
(VII)	146	(B/E)	50	$C_{17}H_{20}O_5$	67.00	6.52	-	67.10	6.57	-
(VIII)	201	(E)	40	$C_{17}H_{18}O_4$	70.96	5.98	-	71.32	6.29	-
(IXa)	267	(E)	80	$C_{19}H_{20}O_3N_2$	70.71	6.69	8.94	70.37	6.17	8.64
(IXb)	165	(B)	75	$C_{21}H_{25}O_3N_2$	71.69	7.29	7.96	71.38	7.08	7.93
(IXc)	177	(E)	75	$C_{23}H_{22}O_2N_2$	77.12	5.86	7.44	77.09	6.14	9.82
(X)	185	(E)	40	$C_{17}H_{17}O_3N$	72.54	6.22	4.26	72.08	6.00	4.86
(XIa)	152	(E)	50	$C_{18}H_{18}O_3N_2$	70.20	5.36	9.39	69.67	5.80	9.03
(XIb)	168	(B)	55	$C_{18}H_{18}O_2N_2S$	66.12	5.38	8.11	66.25	5.52	8.58
(XIc)	184	(B)	65	$C_{25}H_{24}O_2N_2S$	72.12	6.05	6.36	72.11	5.76	6.73
(XId)	172	(A)	50	$C_{20}H_{20}O_4N_2$	67.86	5.22	7.84	68.18	5.68	7.95

*A = Acetic acid B = Benzene E = Ethanol
P = Pet. ether (b.p. 80-100°C)

The solid product obtained after concentration and cooling were crystallized from ethanol to give (Va and b) and (IXa-c) as yellow crystals (cf. Table 1).

Reaction of (II) and (VIII) with hydroxylamine hydrochloride: Formation for (VI) and (X)

A mixture of (II) or (VIII) (0.01 mole), hydroxylamine hydrochloride (0.02 mole), sodium acetate (0.5 g) and ethanol (15 ml) was refluxed for 4 hours. The solid products obtained after concentration and cooling were crystallized from proper solvent to give the corresponding isoxazole derivatives (VI) and (X) respectively (cf. Table 1).

Reaction of (I) with acetylacetone. Formation of (VII)

A mixture of (I) (0.01 mole), acetylacetone (0.01 mole) and sodium metho-

Table-2: The infrared spectra of new compounds

Compound	Group frequencies (KBr; cm^{-1})
(II)	νO=O (1700,1680) and epoxide at (1250)
(IIIa)	νC=O (1685,1670), ν NH or νOH (3298), ν C=C (1605)
(IV)	νC=O (1720,1670), ν NH or νOH (3460), ν C=C(1590)
(Vb)	νC=O (1710), ν C=N (1650), νOH(3360), ν C=C (1600)
(VI)	νC=O (1725), ν C=N (1640), νOH(3520), ν C=C (1685).
(VII)	νC=O (1720, 1700, 1685), νCH_2 (2980), ν OH (3420).
(VIII)	νC=O (1725,1675), ν CH_2 (2920), νOH (322), νC=C (1600).
(IXb)	νC=N(1650), νCH_2(2850, 2910, 2940), ν OH (3180).
(X)	νC=O (1710, 1720), νC=N (1650), ν CH_2 (2900), ν C=C (1580).
(IXa)	νC=O (1710, 1720), νC=N (1690), ν OH,NH (3340), ν CH_2 (2940).
(XIb)	νC=O (172), ν C=N (1660), νOH,NH (3260), νC=S (1350), CH_2 (2920).
(XIc)	νC=O (1720), ν C=N (1680), ν OH,NH (3420), ν C=S (1330), CH_2 (2910).
(XId)	νC=O (1700), ν C=N (1670), ν OH,NH (3300, 3410), ν CH_2 (29)).

xide solution (0.015 mole) was kept at room temperature for 48 hours. The reaction mixture was poured into water and then extracted with ether. The aqueous layer was acidified with ice cold dilute hydrochloric acid. The solid obtained was crystallized to give (VII) as colourless crystals. (cf. Table 1).

Ring closure of (VII): Formation of (VIII)

A mixture of (VII) (0.01 mole) and sodium methoxide (0.015 mole) was fused in an oil bath at 160-170°C for 3 hours. The solid obtained was crystallized from ethanol to give (III) as yellow crystals (cf. Table 1).

Alternate synthesis of (VIII)

A mixture of (I) (0.01 mole), acetylacetone (0.01 mole) and sodium methoxide (0.015 mole) was fused in an oil bath at 160-170°C for 5 hours. The solid compound obtained was crystallized from ethanol to give a product proved to be (VIII) by melting point, mixed melting points determination and comparative spectral data.

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