Cyclisation of Substituted 3-Butenoic Acids, part V[1]. Synthesis and Biological Investigation of New Naphthoic Acids, Benzofluorenones and Thiocarbamates.

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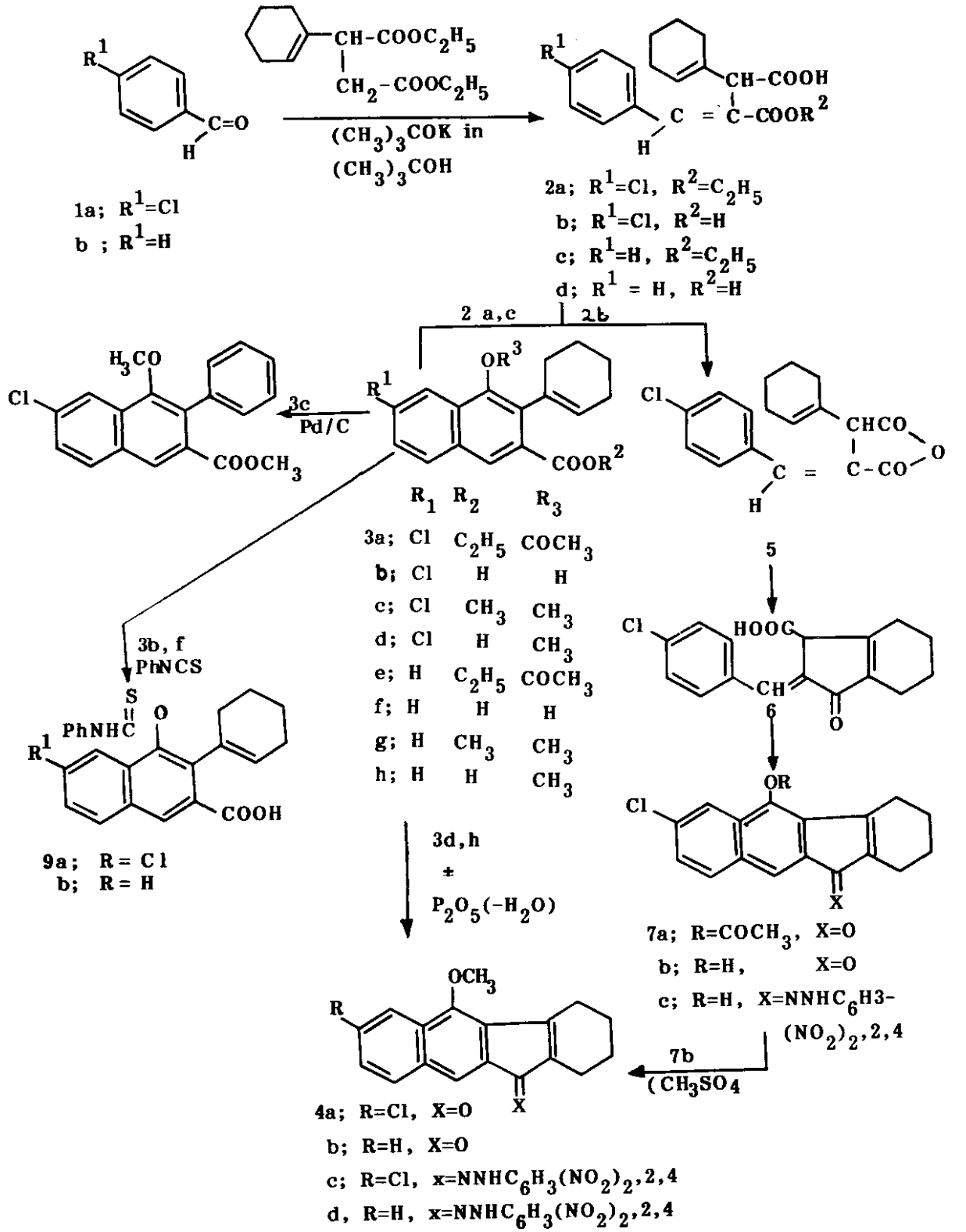
Summary: p-Chlorobenzaldehyde and benzaldehyde are condensed with diethyl-cyclohex-1-enyl succinate in the presence of potassium t-butoxide to give trans(C_6H_4Cl/COOEt)-half-esters. Saponification gave the corresponding dibasic acids. The half-esters are cyclised to acetoxy-naphthoates which afforded the corresponding hydroxy- and methoxy-naphthoic acids. Benzofluorenones (4a,b) are obtained from the methoxynaphthoic acids on treatment with phosphorous pentoxide. The diacid (2b) is converted to p-chlorobenzylidene-1,2,3,4-tetrahydroindanone which is cyclised, saponified and methylated to give the same methoxybenzofluorenone (4a). The biological evaluation of these compounds is discussed and showed a good activity against bacterial strains.

Butenoic acid derivatives exhibit antibiotic action [2]. Naphthol derivatives are known to exhibit antimicrobial activity against pathogenic bacteria and fungi [3]. This prompted us to extend previous investigations [1] to synthesise new butenoic acids, naphthoic acids, benzofluorenone and benzylidene indanone derivatives. All compounds were subjected to biological screening. Most of them were proved to have antimicrobial effect against some gram positive and gram negative bacteria (cf. experimental part).

Stobbe condensation of p-chlorobenzaldehyde and benzaldehyde with diethylcyclohex-1-enyl succinate in the presence of potassium t-butoxide gave the corresponding trans-(Ar/COOEt)-half-esters (2a,c) in about 45% yield. The position of the double bond in the half-esters (2a,c) was established by oxidation with potassium permanganate to the original aldehyde. Saponification of the half-esters (2a,c) gave the diacids (2b,d). Oxidation of the diacids (2b,d) to the original aldehydes indicated that no double-bond shift occurred during hydrolysis. The ir spectra of (2a-d) revealed characteristic band for C=O of esters and acids (see Table 1).

The trans-(Ar/COOEt)-relationship of the half-esters (2a,c) was revealed by their conversion into naphthoic acid derivatives (3). Thus, cyclisation of the half-esters (2a,c) with sodium acetate in acetic anhydride gave ethyl 4-acetoxy-naphthoates (3a,e), respectively. These upon saponification afforded the hydroxy-naphthoic acids (3b,f), which were methylated with dimethyl sulphate and potassium carbonate to give the methoxy-naphthoic esters (3c,g). Subsequent saponification of (3c,g) gave the methoxy-naphthoic acids (3d,h). The ir spectra of the naphthoic acid derivatives (3a-h) show characteristic bands for νC=O (esters and acid groups), νC-O, νC=O for acetoxy groups in the spectra of (3a,e) and νOH which appeared in the spectra of the hydroxy-naphthoic


1a; R1=Cl
b ; R1=H
(CH3)3COK in
(CH3)3COH
2a; R1=Cl, R2=C2H5
b; R1=Cl, R2=H
c; R1=H, R2=C2H5
d; R1 = H, R2=H
2 a,c
2b
3c
Pd/C
R1 R2 R3
3a; Cl C2H5 COCH3
b; Cl H H
c; Cl CH3 CH3
d; Cl H CH3
e; H C2H5 COCH3
f; H H H
g; H CH3 CH3
h; H H CH3
5
6
3b, f
PhNCS
9a; R = Cl
b; R = H
3d,h
±
P2O5(-H2O)
7a; R=COCH3, X=O
b; R=H, X=O
c; R=H, X=NNHC6H3-(NO2)2,2,4
7b
(CH3SO4
4a; R=Cl, X=O
b; R=H, X=O
c; R=Cl, x=NNHC6H3(NO2)2,2,4
d, R=H, x=NNHC6H3(NO2)2,2,4

acids (3b,c) and disappeared in the spectra of the methoxy-naphthoic acids (3d,g) (Table 1). The structure assigned to these compounds (3a-h) was also supported by their electronic spectra which show the absorption bands of naphthoic acid derivatives [1c,4] (Table 2).

Further cyclisation of the methoxy-naphthoic acids (3d,h) occurred when heated with phosphoric oxide in dry benzene to give the corresponding methoxy-benzofluorenones (4a,b) as an oily product, failed to solidify and identified as their 2,4-dinitrophenylhydrazones (4c,d). The electronic absorption spectrum of (4c,d) showed maxima very similar to those reported for benzofluorenone derivatives [5] (Table 2).

Evidence that the dibasic acid (2b) has the same geometrical configuration as the half-ester (2a) was gained from its conversion by another series of reactions to the same methoxy-benzofluorenone derivative (4a). Thus, the dibasic (2b) was dehydrated by acetyl chloride to its anhydride (5) which failed to solidify as it was quickly decomposed to the dibasic acid. Cyclisation of the crude anhydride using anhydrous aluminium chloride in nitrobenzene gave the benzylidene-indanone (6) in almost quantitative yield. The structure assigned to benzylidene-indanone derivative (6) was inferred from, (a) its yellow colour, (b) solibility in sodium carbonate solution (c) its red crystalline DNP and (d) appearance of ir bands for ν C=O of acids and α,β-unsaturated five membered cyclic aryl ketones [6a,7] and a band for two adjacent hydrogen atoms [6b] (Table 1).

The benzylidene-indanone derivative (6) was further cyclised using sodium acetate in acetic anhydride to give acetoxy-benzofluorenone derivative (7a) as an oily product which was difficult to solidify and identified as its red crystalline DNP. The acetoxy-benzofluorenone derivative (7a) was directly saponified to give hydroxy-benzofluorenone (7b). The structure of the hydroxy-benzofluorenone (7b) was established from (a) its orange colour, (b) its ir spectrum which showed bands for ν OH and νC=O of fluorenone [6a,7] and (c) the formation of red crystalline DNP (7c). The ir spectrum of this DNP showed bands for OH and NH. The absence of the band for C=O group supports the assigned structure of the DNP (7c) (Table 1).

Methylation of the hydroxy-benzofluorenone derivative (7b) with dimethylsulfate gave the methoxy-benzofluorenone (4a) as an orange product. Its DNP was identical with the DNP of that methoxy-benzofluorenone obtained by the cyclisation of methoxynaphthoic acid (4a) with phosphoric oxide.

The conversion of the half-ester (2a) and the corresponding dibasic acid (2b) to the same methoxy-benzofluorenone (4a), by two different routes, indicates that they have the same stereochemical configuration and that no isomerisation occurred during hydrolysis.

Aromatisation of cyclohexenyl group to phenyl group occurred when the methoxy-ester (3c) was heated with palladised charcoal (10%) to give the phenyl-naphthoate derivative (8). The structure assigned to this compound (8) was inferred from its ir spectrum which showed characteristic bands of out-of-plane bending frequency of 5 adjacent aromatic H-atoms in addition to a band of ν C=O of the ester group (cf. Table 1).

The N-phenyl thiocarbamates (9a,b) were obtained on treatment of the hydroxy-naphthoic acids (3b,f) with phenyl isothiocyanate in boiling benzene in the presence of triethylamine. The structures of these compounds (9a,b) were established from the spectral data (cf. Table 1). The electronic absorption spectra showed maxima very similar to those reported for naphthoic carbamates [1c,8]. The ir spectra showed bands for νNH and νC=O of aromatic acids [6c] (Table 1).

The formation of the two paraconic esters (10) and (11) arise from the attack of the carbonyl group by

Table-1

Microanalytical data and infrared spectra (KBr disc) of the compounds 2,3,4,6,7,8 and 9.

Compound	M.p.°C (Solv.)	Yield (%) Colour	Molecular formula	Analysis % Calcd.	Found	Infrared spectra (cm^{-1})
2a	220-1* (W+E)	43 Colourless	$C_{19}H_{21}ClO_4$	C 65.42 H 6.03 Cl 10.10	65.10 5.60 9.90	1685 (νC=O)
2b	233-5 (W+E)	93 Colourless	$C_{17}H_{17}ClO_4$	C 63.65 H 5.36 Cl 11.08	63.80 5.10 11.00	1685 (νC=O)
2c	119-21 (P)	32 Colourless	$C_{19}H_{22}O_4$	C 72.60 H 7.10	72.40 7.30	1685 (νC=O)
2d	197-9 (W+E)	77 Colourless	$C_{17}H_{18}O_4$	C 71.33 H 6.29	71.60 6.40	1685 (νC=O)
3a	195-6 (P)	96 Colourless	$C_{21}H_{12}ClO_4$	C 67.65 H 5.64 Cl 9.53	67.20 5.20 9.80	1760 (νC=O) 1220 (νC-O) 1685 (νC=O)
3b	223-5 (B+P)	87 Colourless	$C_{17}H_{15}ClO_3$	C 67.44 H 4.96 Cl 11.74	67.90 5.30 12.00	1710 (νC=O) 3400 (νOH)
3c	175-6 (B+P)	85 Colourless	$C_{19}H_{19}ClO_3$	C 68.99 H 5.57 Cl 10.74	68.60 5.30 10.50	1730 (νC=O)
3d	207-8 (B+P)	86 Colourless	$C_{18}H_{17}ClO_3$	C 68.20 H 5.36 Cl 11.20	68.10 5.46 11.00	1685 (νC=O)
3e	144-6 (B+P)	86 Colourless	$C_{21}H_{22}O_4$	C 74.56 H 6.51	74.50 6.30	1220 (νC-O) 1765 (νC=O) 1720 (νC=O)
3f	185-6 (H)	87 Colourless	$C_{17}H_{16}O_3$	C 76.12 H 5.97	75.80 5.80	1685 (νC=O) 3450 (νOH)
3g	oil					
3h	160-1 (B+P)	70 Colourless	$C_{18}H_{18}O_3$	C 76.60 H 6.38	76.30 6.70	1700 (νC=O)

* W=Water, E=Ethanol, B=Benzene, P=Petroleum ether (b.p. 60-80°C) H=n-Hexane.

Table-1 (cont'd.)

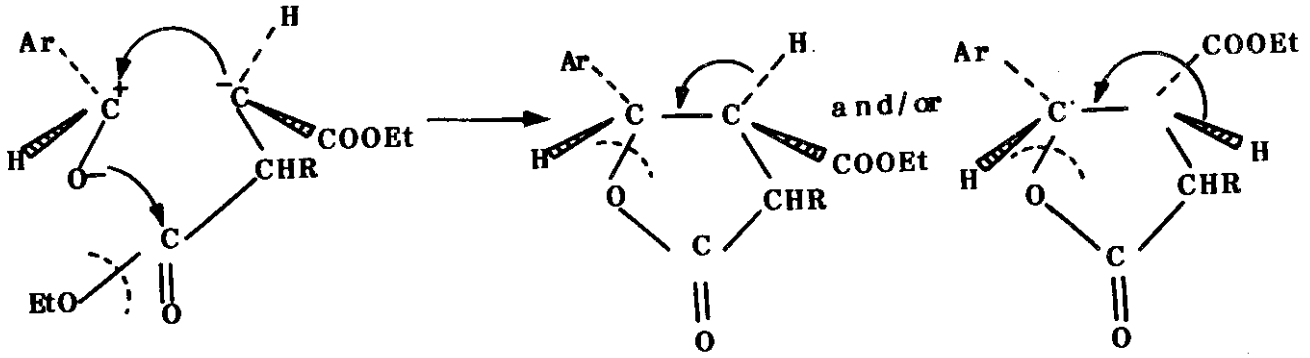
Compound	M.p.°C (Solv.)	Yield (%) Colour	Molecular formula	Analysis % Calcd.	Found	Infrared spectra (cm^{-1})
4c	130-1 (E)	-- (red)	$C_{24}H_{19}ClN_4O_5$	C 60.10 H 3.97 Cl 7.40 N 11.70	60.20 3.80 7.50 11.50	3280 (νNH)
4d	175-7 (E)	-- (red)	$C_{24}H_{20}N_4O_5$	C 64.86 H 4.50 N 12.60	64.60 4.40 12.50	3300 (ν NH)
6	206-7 (B+P)	60 Colourless	$C_{17}H_{15}ClO_3$	C 67.40 H 4.95 Cl 11.70	67.50 4.80 11.60	1690 (ν C=00 850 (Ar H) 750 (Ar H)
7b	300 (B+P)	68 (yellow)	$C_{17}H_{13}ClO_2$	C 71.70 H 4.57 Cl 12.47	71.60 4.70 12.50	1700 (νC=0) 3450 (νOH)
7c	160-1 (E)	-- (yellow)**	$C_{23}H_{17}ClN_4O_5$	C 59.40 H 3.65 Cl 7.60 N 12.09	59.50 3.50 7.70 12.20	3460 (νOH) 3280 (νNH)
8	176 (B+P)	72 Colourless	$C_{19}H_{15}ClO_3$	C 69.86 H 4.50 Cl 10.90	69.70 4.60 10.80	1725 (νC=0) 750, 705 (Ar 5H)
9a	145-6 (E)	83 Colourless	$C_{24}H_{20}ClNO_3S$	C 65.80 H 4.57 Cl 8.10	65.60 4.66 8.00	1680 (νC=0) 3375 (νNH) 1220 (νC=S)
9b	110-2 (B+P)	77 Colourless	$C_{24}H_{21}NO_3S$	C 71.46 H 5.20 N 3.47 S 7.89	71.60 5.00 3.60 8.00	1690 (νC=0) 3280 (νOH) 1220 (νC=S)

** Its solution in water is deep red.

the initially formed carbanion derived from succinic ester either by a two step mechanism as reported by Johnson et.al [9] or by a one step mechanism (concerted mechanism) [1c,5].

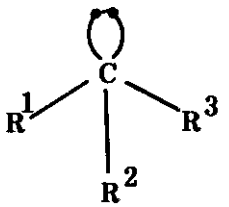
Carbanions which are not stabilised by resonance possess an SP^3 hybridised structure (12) with the unshared pair occupying the apex of the tetrahedron. The umbrella effect exists here so that the unshared pair and the central carbon rapidly oscilate from one side of the plane to the other [10].

Since the carbanion formed by the action of $KOC(CH_3)_3$ in t-butanol probably occures in the solvated form (13) and (14) [11], then they attack the carbonyl group of the aldehyde



a, $Ar=C_6H_4-Cl$, R=

b, $Ar=C_6H_5$, R=



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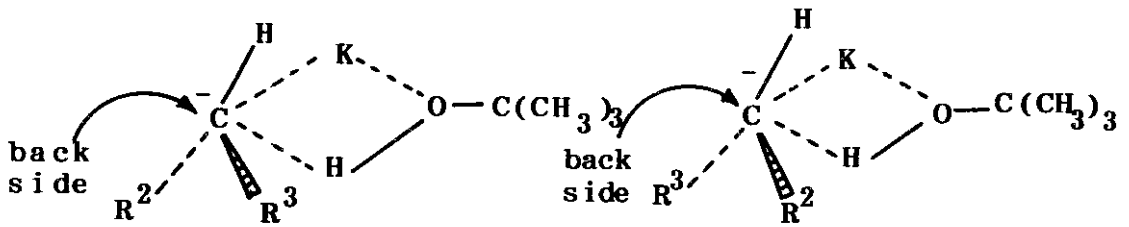
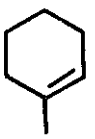


13 14



$R^2 = COOC_2H_5$, $R^3 = CH-COOC_2H_5$

by their back side to give the two paraconic esters (10), (obtained from 14), and (11), (obtained from 13).

The results of this investigation show beyond doubt that polar non-bonded interactions existing between the groups attached to the carbonyl group of the ketone and the carbanion, are more effective than steric factors. The paraconic ester with the least repulsion between the negatively polarised carbonyl group of the ethoxycarbonyl in the succinic ester and the phenyl group of the aldehydes (1a,b), i.e. paraconic esters (10a,b),

which form the half-esters (2a,c), should be more readily formed than their isomers (11a,b).

The present investigation showed that most of the compounds under test were effective against gram positive and gram negative bacteria. The half-ester (2c) and diacids (2b,d) gave slight activity against E.coli.

Cyclisation of the half-esters followed by saponification gave hydroxy-acids which were inactive against gram negative bacteria. They behave differently against gram positive strains. For example the hydroxy-acid (3f) gave slight activity against Staphylococcus aureus. Converting the hydroxy-acids (3b,f) to their corresponding thiocarbamate derivatives (9a,b) established the activity against gram positive bacteria only. They gave a marked activity against S.aureus. Methylation of the hydroxy-acids (3b,f) afforded an inactive methoxy-esters (3c,g). Only methoxy-ester (3c) gave slight activity against the gram positive S.aureus.

Benzofluorenone derivatives gave medium activity against the bacterial strains. It is of interest to note that the hydroxy-benzofluorenone (7b), which gave medium activity against all bacteria, loses its activity completely when converted to its 2,4-dinitrophenylhydrazone (7c). The activity is reestablished again with the methoxy-fluorenone derivative (4c). The other methoxy-fluorenone derivative (4d) gave slight activity against gram positive Bacillus subtilis only.

The results were expressed using the following arbitrary scale:

upto 0 cm = negative (-)
upto 1 cm = slight activity (+)
upto 2 cm = medium activity (++)
upto 3 cm = marked activity (+++)

Table-2: Electronic spectra of naphthoic esters (3a,c), acids (3f,h), benzofluorenones (4c,d) and thiocarbamates (9a,b) (in methylene chloride).

	Band I (^1B_b)		Band II (^1L_a)		Band III (^1L_b)	
Compound	λ_{max} (nm)	ε	λ_{max} (nm)	ε	λ_{max} (nm)	ε
3a	222	52520			360	11180
	255	35540				
3c	220	30400				
	254	16530				
3f	219	39100			339	2300
	214	28740				
3h	221	63230	272	37300	308	2220
4c	226	52160			350	67950
	257	44500				
4d	248	76370	290	39070	395	71040
9a	220	75950	290	36670		
	254	113930				
9b	225	98300				
	241	103170				

Antimicrobial activity of some butenoic acids, naphthoic acids and thiocarbamates:

The gram positive bacteria used in this study are Bacillus subtilis and Staphylococcus aureus and the gram negative bacteria are Pseudomonas auregenosa and Escherchia coli.

Ten mg of the compound were dissolved in one ml of dimethyl-sulphoxide. The microorganisms were cultured on nutrient broth and nutrient agar media. The antibacterial effect of the selected compounds was determined by the Kirby Bauer filter paper disc method [12]. A full platinum loop containing each of the bacterial strain was cultured in 10ml of the nutrient broth and incubated at 37°C for 24 hr. Nutrient agar plates were prepared and incubated for 24 hr to test stirility.

Broth cultures of each of the bacterial strain at a proper dilution was spread onto the surface of the agar in the nutrient agar plates and then allowed to dry for 5 min. Filter paper discs (6 ml diam.), saturated with the solution of each tested compound, were gently applied on to the agar using sterilised forceps. Control plates for the solvent were compared with the tested compound. All plates were incubated at 37°C for 48 hr, then the inhibition zones caused by various compounds on the tested strain were measured to the nearest millimeter.

The results of the investigation are illustrated in Table 3.

Experimental

IR spectra (KBr discs) were recorded on a Schimadzu 408-IR Spectrophotometer, and UV spectra (in methylene chloride) on a spectronic 2000 Spectrophotometer.

Synthesis of substituted 3-butenoic acids (2a,c):

General procedure for Stobbe condensation:

A mixture of the aldehyde (1a,b) (0.1 mol) and diethyl cyclohex-1-enyl-succinate (0.1 mol) in t-butanol (20 ml) was added during 15 min to a boiling stirred solution of potassium t-butoxide in t-butanol (from 5.5g potassium in 140 ml t-butanol). Heating was continued for a further 55 min and most of the alcohol was removed under reduced pressure. The residue was acidified and extracted with ether. The acid fraction was isolated with sodium carbonate solution (10%), acidified with ice-cold hydrochloric acid, extracted with ether, washed with water, dried and the ether removed. Trituration of the oily products with petroleum ether (b.p. 60-80°C) gave solid half-esters crystallised from the suitable solvents to give trans-(p-ClC_6H_4/$COOC_2H_5$)-4-(p-chlorophenyl)- (2a) and trans-(C_6H_5/$COOC_2H_5$)-4-phenyl-2-(cyclohex-1-enyl)-3-ethoxycarbonyl-but-3-enoic acid (2c) (see Table 1).

Saponification of the half-ester:

The half-esters (2a,c) (1g) were refluxed for 2-3 hr with 10% aqueous solution of sodium hydroxide (15 ml) and worked up as usual. The resulting products were crystallised from the suitable solvents to give the corresponding dibasic acids (2b,d) (cf. Table 1).

Oxidation of the half-esters (2a,c) and the dibasic acids (2b,d):

A stirred solution of these compounds (2g) in 20% sodium carbonate solution was oxidised by portion-wise addition of 2% potassium permanganate solution until the colour

Table-3: Antimicrobial activity of some half-esters, diacids, naphthoic acids, benzofluorenone and thiocarbamate derivatives against bacteria strains.

Compound	Gram +ve		Gram -ve	
	Bacillus subtilis	Staphylococcus aureus	Pseudomonas auregenosa	Escherchia coli
2b	-	-	-	+
2c	-	-	-	+
2d	+	+	+	-
3b	-	-	-	-
3f	-	+	-	-
9a	+	+++	-	-
9b	-	++	-	-
3c	-	+	-	-
3g	-	-	-	-
7b	++	++	+	++
7c	-	-	-	-
4c	++	-	++	-
4d	+	-	-	-

persisted (about 45 ml). The reaction mixture was left at room temperature for further 2 hr and worked up as usual. In each case the neutral oxidation product proved to be the corresponding aldehyde when tested with 2,4-dinitrophenylhydrazine.

Synthesis of Naphthoic Acids (3):

Cyclisation of the half-esters (2a,c) to acetoxy-naphthoates (3a,e):

A mixture of the half-ester (0.01 mole) and freshly fused sodium acetate (0.018 mole) in acetic anhydride (50 ml) was refluxed for 5 hr. The oily neutral acetoxy-naphthoates (3a,e) were isolated as usual, triturated with petroleum ether (b.p. 60-80°C) and the solids obtained were crystallised from the suitable solvent to give ethyl 4-acetoxy-6-chloro- (3a) and ethyl 4-acetoxy-3-(cyclohex-1-enyl)-2-naphthoate (3e) (Table 1).

Preparation of the hydroxy-naphthoic acids (3b,f):

The acetoxy-naphthoates (3a,e) were hydrolysed by refluxing with 10% aqueous sodium hydroxide solution (15 ml per gram ester) for 3 hr to give the corresponding hydroxy-naphthoic acids (3b,f) (see Table 1).

Methoxy-esters (3c,g) and methoxy-acids (3d,h):

A mixture of the hydroxy-naphthoic acids (3b,f) (0.01 mole), dimethyl sulphate (9g), anhydrous potassium carbonate (12g), and dry acetone (90ml) was refluxed for 10 hr. The neutral products were isolated as usual. The methoxy-esters (3c,g) were crystallised from the suitable solvents (Table 2).

The methoxy-esters (3c,g) (3 g) were refluxed for 3 hr with 10%

aqueous sodium hydroxide solution (60 ml) to give the corresponding methoxy-acids (3d,h) (cf. Table 1).

Conversion of the dibasic acid (2b) into 3-carboxy-2-(p-chloro-benzylidene)-4,5,6,7-tetrahydroindan-1-one (6):

The dibasic acid (2b) (3 g) was refluxed for 2 hr with acetyl chloride (70 ml) to give the anhydride (5) which failed to solidify. Powdered anhydrous aluminium chloride (3 g) was added to the stirred ice-cold solution of the crude anhydride in dry nitrobenzene (25 ml) and stirring was continued for 4 hr. The mixture was then left for 2 days at room temperature with occasional sitrring. The product was decomposed with ice-cold dilute hydrochloric acid, and the nitrobenzene was steam distilled. The residue after filtration and washing with water was digested with sodium hydroxide solution and the alkaline extract (charcoal) was cooled and acidified with ice-cold hydrochloric acid. The precipitated acid was filtered off and crystallised from the suitable solvent to give the benzylidene-indanone derivative (6) (see Table 1).

Cyclisation of the benzylidene-indanone derivative (6):

A mixture of the benzylidene-indanone derivative (6) (1.2g) and freshly fused sodium acetate (0.6 g) in acetic anhydride (20 ml) was refluxed for 5 hr and the neutral product was isolated as usual to give 5-acetoxy-7-chloro-1,2,3,4-tetrahydro -11H-benzo[e]fluoren-11-one (7a) (cf. Table 1).

Methoxy-benzofluorenones (4a,b):

Method (I):

A solution of the 3-(cyclohex-1-enyl)-4-methoxy-naphthoic acids (3d,h) (1.4 g) in dry bebnzene (50 ml) was refluxed with phosphoric oxide (9 g) for 2 hr. The benzene was removed under reduced pressure and the residue was cooled and decomposed with water. The orange products were worked up as usual to give the methoxy-benzofluorenones (4a,b) (cf. Table 1).

Method (II):

The acetoxy-benzofluorenone (7a) (0.01 mole) was hydrolysed with 10% aqueous sodium hydroxide solution (50 ml) to give the 7-chloro-5-hydroxy-1,2,3,4-tetrahydro-11H-benzo-[e] fluoren-11-one (7b) (cf. Table 1).

The hydroxy-benzofluorenone (7b) (0.01 mole) was methylated by refluxing for 12 hr with a mixture of dimethyl sulphate (9 g) anhydrous potassium carbonate (12 g) and dry acetone (80 ml). The red product was crystallised from the suitable solvent to give the above methoxy-benzofluorenone (4a) obtained by method (I). It gave 2,4-dinitrophenyl-hydrazone undepressed when admixed with an authentic sample (Table 1).

Preparation of methyl 6-chloro-4-methoxy-3-phenyl-2-naphthoate (8):

The methoxy-ester (3c) (0.7 g) was mixed with dry 10% palladium-carbon catalyst (0.4 g) and heated to about 200°C with frequent stirring for 3 hr. The reaction mixture was cooled, dissolved in ether and filtered. The dry ethereal solution (Na_2SO_4) was evaporated and the residual oil solidified on trituration with petroleum ether (b.p. 40-60°C) and few drops of ether. It was crystallised from the suitable solvent to give the phenyl-naphthoate (8) (see Table 1).

Preparation of N-phenyl thiocarbamates (9a,b):

A mixture of the hydroxy-naphthoic acids (3b,f) (0.01 mole), phenyl isothiocyanate (0.01 mole) and 3 drops

of triethylamine in dry benzene (30 ml) was refluxed for 5 hr. Benzene was removed under reduced pressure and the residue triturated with light petroleum (60-80°C) to get a solid crystallised from the suitable solvent to give N-phenyl thiocarbamates (9a,b) (cf. Table 1).

Acknowledgement

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