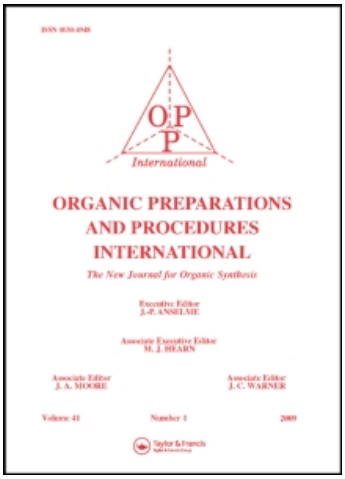

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SYNTHESIS OF POTENTIALLY BIOLOGICALLY ACTIVE COMPOUNDS *via* THE STOBBE CONDENSATION

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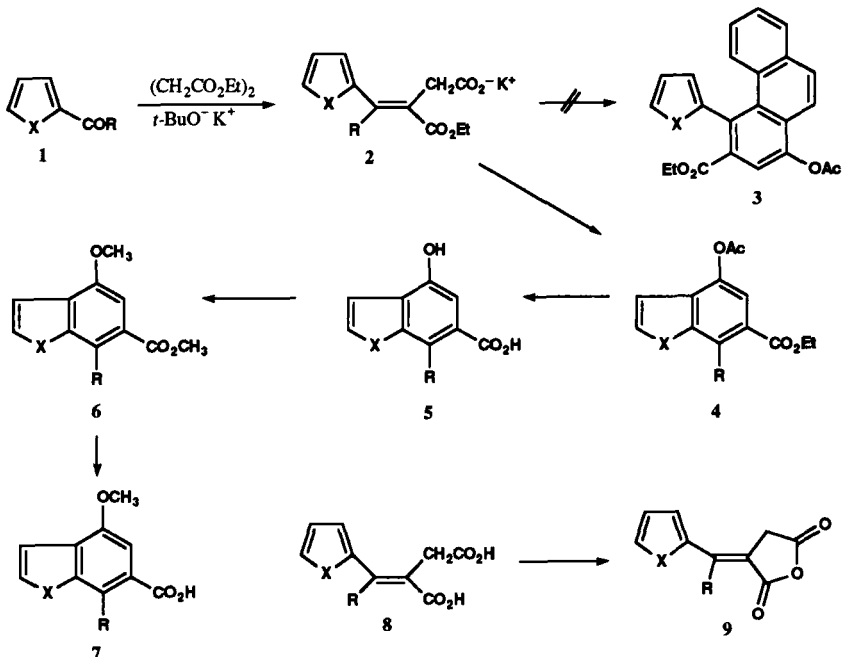
Butenoic acid derivatives[1] exhibit antibiotic activity. Naphthol[2a] and benzothiophene[2b] are reported to have antimicrobial activity against pathogenic bacteria and fungi. In conjunction with our current research on the Stobbe condensation,[3] heterocyclic naphthyl ketones (**1**) were condensed with diethyl succinate to yield the (E) half-esters of but-3-enoic acid derivatives (**2**). They were subjected to a series of reactions to give benzothiophene or benzofuran 1'- (or 2'-) naphthyl derivatives (**4-7**).

1-Naphthyl-2'-thienyl-, 1-naphthyl-2'-furyl-, 2-naphthyl-2'-thienyl- and 2-naphthyl-2'-furyl ketones (**1**) were prepared by Friedel-Crafts condensation of 1- or 2-naphthoyl chlorides with thiophene and furan in dichloromethane in presence of stannic chloride (~ 85%);[4] lower yields were

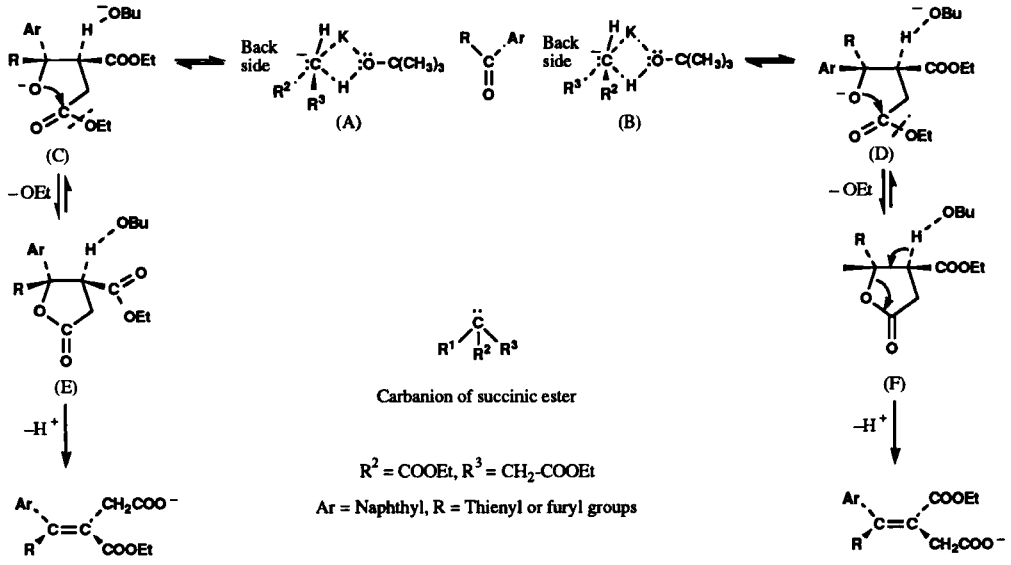


a, X = S; R = 1-Naphthyl b, X = O; R = 1-Naphthyl
c, X = S; R = 2-Naphthyl d, X = O; R = 2-Naphthyl

obtained (~ 50%) with aluminum chloride.[5] The condensation of these thienyl and furyl naphthyl ketones with diethyl succinate in the presence of potassium *t*-butoxide gave predominantly the corresponding (E)-half-esters (**2a-d**)[6] (*i. e.* CO_2Et group and heterocyclic ring in ***trans***-positions).

Evidence for the (E)-configuration of the half-esters was provided by their cyclization to the corresponding benzothiophene or benzofuran derivatives (**4**) rather than to the phenanthrenes (**3**). The structure of **4a** was substantiated from the analytical and spectral data. Its IR spectrum displayed strong bands at 1750 and 1270 cm^{-1} (acetoxyl group) and at 1690 cm^{-1} (>C=O of aromatic ethoxycarbonyl group. The ^1H NMR showed a two proton doublet belonging to AB system ($\Delta\delta/J$ = 9.5 Hz) at δ 7.5 and 7.31 due to C_2 and C_3 hydrogens (of thiophene) respectively, with $J_{2,3} = J_{5,6,7}$ = 6 Hz, confirming the benzothiophene structure. Signals at δ 0.56 (3H, t, *J* [~7.2] CO_2CH_2-$\underline{CH_3}$), 2.47 (3H, s, $OCO\underline{CH_3}$), 3.81 (2H, q, *J* [~7.2] $CO_2\underline{CH_2}$-CH_3) and 7.23-7.9 (10 H, m, Ar-H) are also present in the spectrum. The mass spectrum of **4a** showed M^+ 390 (34%), 348 (100%), 320 (10%), 303 (29%), 274 (10%), 221 (2%) and 127 (3%). No fragments with m/e 215 or 83 were obtained which suggests that the structure should be a benzothiophene and not a thienylphenanthrene derivative. The electronic spectrum resembles that of a 1,1'-binaphthyl derivative (λ_{max} at 228, 283 nm) and not that of 4-arylphenanthrene derivative (λ_{max} at 223, 260 nm).[8a] The predominance of the (E) configuration of the half-ester can be interpreted in the light of accepted mechanisms.[8a,b]

The predominant E-half esters, obtained by the condensation of arylnaphtyl ketones with diethyl succinate, afforded arylphenanthrene derivatives on cyclization with sodium acetate in acetic anhydride.[3] On the other hand, treatment of thienyl- and of furyl naphthyl ketones under the same conditions gave the corresponding benzothiophene or benzofuran derivatives. The results might be



interpreted as follows. The formation of the two paraconic esters (E) and (F) arise from the attack of the carbonyl group by the initially formed carbanion derived from succinic ester.[8a,b] However, in

t-butanol the carbanion is associated with its cation and solvation through hydrogen bonds at the front side. Abstraction of hydrogen from hydrogen-bonded solvent molecules would lead to products of retained configuration.[10] Since the carbanions formed by $KOCMe_3$ in *t*-butanol probably occurs in solvated[3] forms (A) and (B),[8a] it is more likely that they may attack the carbonyl group of the ketone by their backside to give two paraconic esters (C) and (D). The esters formed are determined by steric factors and/or polar non-bonded interactions existing between the groups attached to the carbonyl group of the ketone and the carbanion. The results of this investigation show that *polar non-bonded* interactions are more important than *steric* factors. The paraconic ester with the least repulsion between the negatively polarized carbonyl group of the ethoxycarbonyl and the heterocyclic group should be readily formed. Thus, the predominant (E-) half-esters underwent cyclization to the benzothiophene or benzofuran derivatives (**4**) and not to phenanthrenes (**3**).

(E)-3-Carboxy-4-(1- or 2'-naphthyl)-4-(2"-thienyl)- and (2"-furyl) but-3-enoic derivatives **8** showed a more powerful bacteriocidal effect against Gram positive than against Gram negative bacteria and fungi. Those compounds with a free phenol group (**5**) were more effective against Gram positive than against Gram negative bacteria. The antibacterial and antifungal activity are lost when the phenolic and the carboxylic groups are protected as acetoxyl and ester groups. The benzothiophene derivatives were markedly more active than those of benzofuran.

EXPERIMENTAL SECTION

Mass spectra were measured on a Massen Spectrometer Mat 112. NMR spectra were run on a Varian EM 360 L NMR spectrometer. IR (KBr) were measured on a Beckman IR 4220. The electronic spectra were determined in EtOH on a Shimadzy graphic printer Pr-1. Microanalyses were performed by the Microanalytical Units of Cairo University and of the National Research Center.

Stobbe Condensation. General Procedure.- A mixture of ketone (0.1 mol) and diethyl succinate (0.12 mol) in *t*-butanol was gradually added during 1 hr. to a heated solution of potassium *t*-butoxide [(from potassium (5.8 g) and *t*-butanol (85 mL)] at 70-75°. The mixture was kept at this temperature for further 1.5 hr then worked up as usual.[3] The acidic products gave heavy brown oils which could not be crystallized (yield, **2a-b** ~54%, **2c** ~62%). 2-Furyl-2'-naphthyl ketone gave (E)-3-ethoxycarbonyl-4-(2'-naphthyl)-4-(2'-furyl)-but-3-enoic acid (**2d**) as colorless crystals from light petroleum (yield ~ 63%), mp. 175-176° (C=O, 1700-1680 cm^{-1}, -OH 3280-2460 cm^{-1}).

Anal. Calcd. for $C_{21}H_{18}O_3$: C, 72.00; H, 5.14, Found: C, 71.82; H, 5.30

Cyclization of the Half-esters 2a-2d.- A mixture of the half-ester (1 mol), fused sodium acetate (1.2 mol) and acetic anhydride (30 mL/per 1g sodium acetate) was left standing overnight at room temperature with occasional shaking. The temperature was gradually raised to 70-80° over 2 hrs and maintained at this range for 4 additional hrs before the neutral cyclization products were isolated[3] (Tables 1 and 2).

TABLE 1. Elemental Analyses and ^1H NMR Spectra of New Compounds

Cmpd.	mp. (solv.)	Elemental Analyses C	H	N	S	(δ) ppm
1a	68-69 (M)	75.63	4.20	-	13.44	
		75.61	4.21	-	13.25	
1a•DNP[b]	204-205 (A)	60.29	3.35	13.39	7.65	
		60.08	3.40	13.52	7.60	
1b[c]	59-60 (M)	81.08	4.50	-	-	
		81.12	4.43	-	-	
1b•DNP[b]	215-216 (A)	62.69	3.48	13.93	-	
		62.62	3.51	13.91		
1c	87-88 (M)	75.63	4.20	-	13.44	
		75.45	4.21	-	13.78	
1c•DNP[b]	211-212 (A)	60.29	3.35	13.39	7.65	
		60.27	3.30	13.40	7.60	
1d	67-68 (M)	81.08	4.50	-	-	
		80.77	4.57	-		
1d•DNP[b]	208-209 (A)	62.69	3.48	13.93	-	
		62.70	3.40	13.92		
4a	155-156 (M)	70.76	4.61	-	8.20	0.56 (3H, t, J (7.2)
		70.65	4.53	-	8.02	CO_2. $CH_2\underline{CH_3}$
						2.47 (3H,S, O-CO-$\underline{CH_3}$)
						3.81 (2H, q (7.2)
						$CO_2.\underline{CH_2}CH_3$ and
						7.23-7.92 (10H, m, Ar-H)
4b	184-185 (B-P)	73.79	4.81	-	-	1.11 (3H, t, J (7.0)
		73.54	5.10	-		$CO_2.CH_2\underline{CH_3}$
						2.4 (3H,S, O-CO$\underline{CH_3}$)
						3.74 (2H, q, J (7.0)
						CO_2. $\underline{CH_2}CH_3$ and
						6.33-7.93 (10H, m, Ar-H)
4c	112-113 (M)	70.76	4.61	-	8.20	1.10 (3H, t, J (7.0)
		71.01	4.81	-	8.21	CO_2. $CH_2\underline{CH_3}$ and
						2.18 (3H,S, O-CO-$\underline{CH_3}$)
						3.80 (2H, q, J (7.0)
						CO_2. $\underline{CH_2}CH_3$ and
						7.2-7.97 (10H, m, Ar-H)
4d	182-183 (B)	73.79	4.81	-	-	1.22 (3H, t, J (7.0)
		73.88	4.89	-		CO_2. $CH_2\underline{CH_3}$)
						2.42 (3H,S, O-CO-$\underline{CH_3}$)
						3.75 (2H, q, J (7.0)
						CO_2. $\underline{CH_2}CH_3$ and
						6.55-7.97 (10H, m, Ar-H)

TABLE 1. Cont'd

Cmpd.	mp. (solv.)	Elemental Analyses C	H	N	S	(δ) ppm
5a	190-191 (Ac-B)	71.25	3.75	-	10.00	
		71.32	4.01	-	9.75	
5b	241-242 (Ac-B)	75.00	3.94	-	-	
		74.84	3.81	-		
5c	234-235 (Ac-B)	71.25	3.75	-	10.00	
		71.52	4.02		9.92	
5d	218-219 (B-P)	75.00	3.94	-	-	
		74.76	3.65	-		
6a	170-171 (B)	72.41	4.59	-	9.19	3.36 (3H,S, CO.O.$\underline{CH_3}$);
		72.52	4.62	-	9.02	4.06 (3H,S, O.$\underline{CH_3}$), and
						7.20-7.90 (10H, m, Ar-H).
6b	153-154 (P)	75.90	4.82	-	-	3.36 (3H,S,-CO_2-$\underline{CH_3}$);
		75.75	4.80	-		4.07 (3H,S, O-$\underline{CH_3}$), and
						6.40-8.67 (10H, m, Ar-H).
6c	181-182 (B-P)	72.41	4.59	-	9.19	3.37 (3H,S,-CO_2-$\underline{CH_3}$);
		72.61	4.62	-	9.31	4.09 (3H,S, O-$\underline{CH_3}$), and
						7.33-8.01 (10H, m, Ar-H).
6d	154-155 (B-P)	75.90	4.82	-	-	3.52 (3H,S,-CO_2-$\underline{CH_3}$);
		75.91	4.86	-		4.22 (3H,S, O-.$\underline{CH_3}$), and
						6.70-8.03 (10H, m, Ar-H).
7a	257-258 (Ac-B)	71.86	4.19	-	9.58	
		71.65	4.35	-	9.85	
7b	232-233 (B)	75.47	4.40	-	-	
		75.15	4.16	-		
7c	251-252 (B)	71.86	4.19	-	9.58	
		71.82	4.21	-	9.91	
7d	143-144 (Ac-B)	75.47	4.40	-	-	
		75.25	4.32			
8a	130-131 (Ac-B)[d]	72.11	4.81	-	7.69	
		72.36	4.91	-	7.64	
8b	105-106 (Ac-B)[d]	75.00	5.00	-	-	
		74.74	4.78	-	-	
8c	176-177 (Ac-B)	67.45	4.14	-	9.47	
		67.50	4.13	-	9.62	
8d	143-144 (Ac-B)	70.81	4.34	-	-	
		71.10	4.06	-		
9a	171-172 (B)	71.25	3.75	-	10.00	
		71.21	3.72	-	9.84	
9b	160-161 (P)	75.00	3.95	-	-	
		74.93	4.00	-	-	

TABLE 1. Cont'd

Cmpd.	mp. (solv.)	Elemental Analyses C	H	N	S
9c	158-159 (B)	71.25	3.75	-	10.00
		71.42	3.65	-	9.83
9d	168-169 (B-P)	75.00	3.95	-	-
		74.94	3.84	-	-

a) Solvent of crystallization given in parentheses: A = acetic acid; Ac = acetone; B = benzene, H = *n*-hexane; M = methanol; P = pet. ether (40-60°); b) 2,4-Dinitrophenylhydrazone c) Obtained as an oil, bp. 360-363° (see ref. 5); d) Crystallizes with one mole of benzene which could not be removed by heating in vacuum.

TABLE 2. Mass Spectra of **1a**, **4a**, **5a**, **5c** and **5d**

1d	222 (100, $C_{15}H_{10}O^+$),155 (75, $C_{11}H_7O^+$), 95 (29, $C_5H_3O_2^+$), 127 (90, $C_{10}H_7^+$).
4a	390 (34, $C_{23}H_{18}O_4S^+$), 348 (100, $C_{21}H_{16}O_3S^+$), 320 (10, $C_{20}H_{16}O_2S^+$), 309 (29, $C_{19}H_{11}O_2S^+$), 274 (10, $C_{18}H_{10}O^+$), 221 (2, $C_{11}H_9O_3S^+$), 127 (3, $C_{10}H_7^+$).
5a	320 (100, $C_{19}H_{12}O_3S^+$), 303 (20, $C_{19}H_{11}O_2S^+$), 291 (4, $C_{18}H_{11}O_2S^+$), 274 (5, $C_{18}H_{10}OS^+$), 246 (5, $C_{17}H_{10}S^+$) 176 (3, $C_9H_4O_2S^+$), 127 (4, $C_{10}H_7^+$).
5c	320 (100, $C_{19}H_{12}O_3S^+$), 303 (15, $C_{19}H_{11}O_2S^+$), 274 (5, $C_{18}H_{10}OS^+$), 176 (1, $C_9H_4O_2S^+$), 127 (3, $C_{10}H_7$+).
5d	304 (100, $C_{19}H_{12}O_4^+$) 287 (3, $C_{19}H_{11}O_3^+$), 275 (7, $C_{18}H_{11}O_3^+$),247 (13, $C_{17}H_{11}O_2^+$), 160 (1, $C_9H_4O_3$),127 (3, $C_{10}H_7^+$).

Conversion of the Acetoxy Esters 4a-4d into Methoxy Acids (6a-d).- The acetoxy esters **4a-d** were hydrolyzed by refluxing with 10% methanolic potassium hydroxide (15 mL/gm ester) for 3 hrs to give the corresponding phenolic acids (**5a-d**), after cooling and acidification. These acids (1 mol) were methylated by refluxing for 10 hrs with dimethyl sulfate (5 mol) and potassium carbonate (6 mol) in dry acetone. The methoxy esters (**6a-d**) were crystallized from a suitable solvent. Hydrolysis to the corresponding acids was accomplished by refluxing for 3 hrs with 10% methanolic potassium hydroxide (15 mL/1 g ester), followed by cooling and acidification; yield (~ 95%) (Tables 1 and 2).

Saponification of the Half-esters 2a-d to the Corresponding Acids (8a-d).- The half-esters **2a-d** were refluxed for 3 hrs with 10% aqueous alcoholic solution of potassium hydroxide (15 mL/1 gm half-ester). The dibasic acids obtained after acidification were crystallized from a suitable solvent.

Conversion of the Dibasic Acids into their Anhydrides (9a-d).- The acids **8a-d** were refluxed with acetyl chloride (10 mL/g acid) for 3 hrs to give the corresponding anhydrides (**9a-d**) (Table 2).

Antibacterial activity.- Selected compounds were tested *in vitro* at a concentration 10 mg/mL of dimethyl sulfoxide on nutrient broth and nutrient agar media following the Kirby-Bauer filter paper disc method.[2a,9]

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