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Total Synthesis of Monocyclic Pyrimidinium Betaines With Fatty Alkyl Chains

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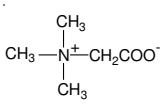
Seven betaines were prepared by condensation of N,N'-diphenylamidines with malonic acid derivatives. The amidines were made *via* a multistep synthesis, starting from their corresponding fatty acids. Malonyl chloride and dipentachlorophenyl phenylmalonate, two derivatives of malonic acid, were obtained from malonic acid and benzyl chloride, respectively. Most of the products were characterized by IR, UV, ^{1}H and ^{13}C NMR. Biological assays of the synthesized betaines revealed their good antibacterial and antifungal activities against the *Pseudomonas aeruginosa*, *Bacillus subtilis* and *Mucor ramannianus* and an activity against *Candida albicans*.

Key Words: Betaine, Biological activity, Cycloaddition, Fatty amidine, Pyrimidine, Amphoteric surfactant.

INTRODUCTION

Betaines are an interesting group of amphoteric surfactants with a zwitterionic form[1]. Over a century ago, the first betaine-type molecule, **1**, an amino acid derivative, was extracted from sugar beet. Later, the term 'betaine' was coined to amphoteric surfactants with a similar structure and having one fatty chain. Based on their physico-chemical and biological properties, betaine-type surfactants found widespread applications[2-4]. While its anionic nature ensures its detergency force, its cationic part is responsible for its bactericidal potency[5]. Betaines bearing imidazoline derivatives, **1'**, have been broadly employed as surface active agents in toilet and cosmetics industry. They are featured with a great stability in alkaline media without undergoing decomposition[6].



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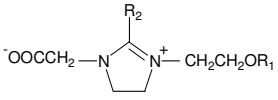
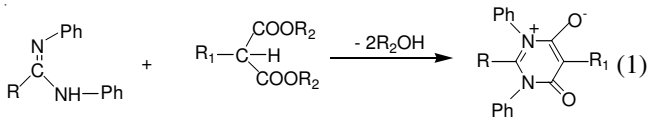


R_1 = H; CH_2COONa
R_2 = Fatty alkyl chain

1'

Because the efficacy of these imidazoline-containing betaines owes mainly to the heterocyclic nature, it is thought useful and interesting as well to extend these betaines to those having a pyrimidine cycle. The interest is doubly faceted as the pyrimidine-based betaines would possess a biological activity owing to this cycle[7] and a potential interfacial power owing to their surfactant structure.

In this paper, we present the results of the synthesis of seven betaines having pyrimidine cycle by condensing the appropriate N,N'-diphenylamidine with the corresponding malonic acid derivative, as depicted in eqn. 1. N,N'-Diphenyl-amidines and malonic acid derivatives were also prepared.



(1)

R = Ph, C_9-C_{17} alkyl groups
R_1 = H, Ph
R_2 = C_2H_5, C_6Cl_5

EXPERIMENTAL

All chemicals and solvents were purchased from Fluka, Merck and Schuchardt. Dichloromethane was dried over anhydrous calcium chloride and distilled over phosphorus pentoxide. Pyridine was dried over potassium hydroxide pellets and distilled over anhydrous barium oxide. TLC plates, made of silica and alumina gels, were supplied by Merck. Infrared spectra were recorded with FTIR Perkin Elmer 457; KBr pellets and nujol were used for crystals and liquids, respectively. UV spectra were taken using PyeUnicam SP8 UV/vis and a double beam Schimadzu UV-vis type 160. ^{1}H

and ^{13}C NMR spectra were realized on Varian 411 spectrometer. Melting points were measured using a Büchi 220 V capillary melting point apparatus.

Synthesis of alkanilides: The alkanilides **3b-f** were prepared according to the Webb procedure[8]. The reactions involved the use of an excess of aniline and the corresponding fatty acids; water was eliminated by distillation. Yields and melting points are compiled in Table-1. The alkanilides were dried in a dessicator before use. The alkalinides were also characterized by different spectral analyses. Overall, their different spectra were identical. As an example, the following are the spectral characteristics of **3c**: IR (KBr, ν_{max}, cm^{-1}): 3300 (NH), 1655 (C = O), 1310 (C-N). UV (cyclohexane), λ_{max} (nm), (ε): 241 (12375). Lit., 241 (15488) [14b]; ^1H NMR ($CDCl_3$), δ (ppm): 7.17-7.45 (NH, H_{arom}), 2.35 (α CH_2), 1.26((CH_2)$_9$), 0.88 (CH_3).

TABLE-1
YIELDS AND MELTING POINTS OF THE DIFFERENT ANILIDES

Anilide	R	Yield (%)	m.p. (ºC); [lit.]
3a	Phenyl	80.0*	163-163.5; 163 [8]
3b	$CH_3(CH_2)_8$–	84.0	64-65
3c	$CH_3(CH_2)_{10}$–	73.0	76-78; 78 [13a]
3d	$CH_3(CH_2)_{12}$–	96.0	83-84; 84 [13a]
3e	$CH_3(CH_2)_{14}$–	74.5	88-90; 91 [13a]
3f	$CH_3(CH_2)_{16}$–	95.5	89-91; 95 [13a]

*80-84 % [8].

Typical synthesis of N,N'-diphenylalkamidines[9a]: With the exception of N,N'-diphenylbenzamidine **4a**, which was prepared according to the method described by Hontz and Wagner[9b], the remaining amidines, **4b-f**, were made as follows: A 250 mL round-bottomed flask fitted with a condenser and a magnetic stirrer, was charged with 7.27×10^{-2} mole of dried alkanilides (**3b-f**), 7.27×10^{-2} mol of phosphorus pentachloride and 10 mL of dried dichloromethane. After stirring the mixture at room temperature for 2 h, the time required for hydrogen chloride to evolve, 7.27×10^{-2} mol of dried pyridine and 7.27×10^{-2} mol of freshly distilled aniline were added. After a 40 min stirring at a room temperature (25 ºC), 19.8 mL of water was poured into the mixture, which was then made alkaline with a 28 % aqueous ammoniacal solution. After this work-up, a white precipitate was formed. The whole heterogeneous mixture was stirred for an additional 45 min. The precipitate was separated from the organic phase by filtration. To enhance the yield, the organic phase was separated from the aqueous one by decantation. After drying over anhydrous $MgSO_4$ and evaporation of the solvent, the alkylamidines were isolated as white solid. These N,N'-diphenylalkamidines **4b-f** were purified by recrystallization in 80 % ethanol, affording white needles. Yields and melting points of the different amidines are presented in Table-2. The amidines were also characterized by the spectral analyses and their different spectra were found to be identical. As an example, the following are the spectral characteristics of **4c**: IR (KBr, ν_{max}, cm^{-1}): 3300 (NH), 1635 (C=N), 1345 (C-N). UV (dioxane), λ_{max} (nm), (ε): 264 (17200). ^1H NMR ($CDCl_3$), δ (ppm): 7.14-7.31 (NH, H_{arom}), 2.31(α CH_2), 1.21 ((CH_2)$_9$), 0.87-0.95 (CH_3). ^{13}C NMR ($CDCl_3$), δ (ppm): 14.1-31.9 (C_{alph}), 121.5-129 (C_{arom}), MS: (m/e): 350, 258, 77.

TABLE-2
YIELDS AND MELTING POINTS OF THE DIFFERENT AMIDINES

Amidine	R	Yield (%)		m.p. (ºC); [lit.]
4a	Phenyl	70*		145-145.5; 144-145 [9b]
		25 ºC	40 ºC	
4b	$CH_3(CH_2)_8$–	52	45.5	91-91.5
4c	$CH_3(CH_2)_{10}$–	63	63.5	93-93.5
4d	$CH_3(CH_2)_{12}$–	75	67.1	95-95.5
4e	$CH_3(CH_2)_{14}$–	62	69.7	96-96.5
4f	$CH_3(CH_2)_{16}$–	73	45.1	98-98.5

*87 % [9b].

Synthesis of malonic acid derivatives

Malonyl chloride (6): Malonyl chloride was prepared by the conventional method involving the reaction of malonic acid with thionyl chloride as reported by Raha[10]. Into a 250 mL Erlenmeyer fitted with a condenser linked to a washing flask containing sulfuric acid, were charged 52 g (0.5 mol) of malonic acid (**5**) and 130 mL (1.18 mol) of thionyl chloride. The mixture was stirred for 3 days at 45-50 ºC by means of a water bath. The system became homogenous and turned black-blue. Then, the heating temperature was raised to 60 ºC and maintained for 6 h, followed by cooling to ambient temperature overnight. After removal of excess of thionyl chloride, malonyl chloride was isolated by distillation as a pale yellow liquid. This colour deepened by standing for some days. The weight of the obtained malonyl chloride was 16.5 g, yield 24 % .

Dipentachlorophenyl phenylmalonate 16: First, dried phenylmalonic acid **13** was made in 83 %yield by a multistep synthesis starting from benzyl chloride **7**. Then, the procedure of Huhn *et al.*[11] was applied to the **13** to produce **16** as follows: Into a 250 mL round-bottomed flask equipped with a magnetic stirrer and a condenser on top of which calcium chloride drying tube was placed, were added 7.2 g (0.04 mol) of **13** in 60 mL of dried dichloromethane and 17.6 g (0.08 mol) of phosphorus pentachloride. The mixture was stirred at room temperature for 2 h, giving a clear solution. The dichloromethane and the by-product, phosphoryl chloride, were evaporated by means of rotary evaporator at a temperature of 50 ºC until a constant weight (*ca.* 1 h). The produced acid chloride, 8.9 g, was isolated as a dense yellow-green liquid. By means of a dropping funnel fitted with a calcium chloride tube, the acid chloride in 10 mL of dichloromethane was added dropwise into a solution of 21.3 g (0.08 mol) of pentachlorophenol in 80 mL of dichloromethane, containing 8 mL of anhydrous pyridine. After few minutes, a white precipitate was formed. The suspension was stirred for 24 h at room temperature and then filtered. The precipitate obtained was treated several times with absolute ethanol until it became white. Table-3 compiled the physical properties and the yields of the different malonic acid derivatives. Their IR and UV spectral analyses are given in Tables 4 and 5, respectively.

Synthesis of the different betaines

4*H*-4-Oxo-1,2,3-triphenyl-1-pyrimidinium-6-olate (24): Into a 10 mL round-bottomed flask fitted with a condenser and immersed into an oil bath were charged 1.36 g (5×10^{-3} mol) for N,N'-diphenylbenzamidine **4a** and 1.2 g (7.5×10^{-3} mol) of ethyl malonate **23**. Then, the heat was supplied to the

TABLE-3
YIELDS AND PHYSICAL PROPERTIES OF THE DIFFERENT MALONIC ACID DERIVATIVES

Malonic acid derivative	Aspect	Yield (%) [lit.]	m.p. (ºC) [lit.]	b.p. (ºC)/mmHg [lit.]
6	Faint yellow liquid	24; 72-85 [10]	–	55-57/25; 58-60/287 [10]
8	Clear oil	56; 63-70 [23]	–	205-209/60; 135-140/38 [23]
9	〃	73; 83-87[23]	–	174-180/60; 132-138/32 [23]
10	〃	63; 80-83[24]	–	73/0.02; 106-107/25 [24]
11	〃	73	–	–
12	〃	61; 80-85[24]	–	158-162/10 [25]
13	White crystals	83	150-152; 153-155 [15]	–
14	White needles	37	77-78	–
16	White powder	82; 92[11]	226-230; 215-217 [11]	–

TABLE-4
IR RESULTS OF THE DIFFERENT MALONIC ACID DERIVATIVES

Malonic acid derivative	Characteristic bands (cm^{-1})		Literature
6	1785 ν(C=O)	2925; 1420 (CH_2)	
8	2250 ν(C≡N)		
9	1715 ν(C=O)	1145 (C-O)	1750 ν(C=O); 1140 ν(C-O) [12b]
10	1750 ν(C=O)	1185 (C-O)	
11	1755 ν(C=O)	1260 (C-O); 3500 (OH)	
12	1755 ν(C=O)	1310; 1150 (C-O)	
13	1660 ν(C=O)	1280 (C-O); 3300-2500 (OH)	
14	1680 ν(C=O)	1395 (CO_2H); 3000 (OH)	1810; 1880 (ester); 1390-1360
16	1815 ν(ester)	1360; 1390 (pentchlorophenyl)	(pentachlorophenyl) [11]

TABLE-5
UV RESULTS OF THE DIFFERENT MALONIC ACID DERIVATIVES

Malonic acid derivative	Solvent	λ_{max} (nm) (ε)	[Literature]
6	Dioxane	304.2 (244)	304 (372) [26a]
8	Ethanol	257.7 (240.9)	257 (194) [12c]
9	Methanol	258 (204)	–
10	Ethanol	255.5	225 (398) [12d]
11	Cyclohexane	259.5 (3977.2)	–
12	Cyclohexane	258 (3100)	258 (2034) [26b]
16	Dioxane	303.5 (5050)	–

system allowing the temperature to reach 165 ºC. This temperature was maintained for 1 h until ethanol started to distill off. Afterwards, the temperature was allowed to rise up to 185 ºC to complete the ethanol distillation. After nearly 3 h of reaction at this temperature, a few crystals were formed within the reaction mixture. The latter was heated further at higher temperature, 190-200 ºC for 2 h. The system was then cooled to room temperature and, finally was allowed to stand inside the refrigerator for overnight. Upon addition of absolute ethanol (a volume twice that of the system) to the thus-cooled system, yellow brown crystals were separated by filtration and washed with a plenty of cold absolute ethanol. The recrystallization of this product from absolute ethanol afforded a powdery white solid. Results are given in Table-6.

Synthesis of 4*H*-4-oxo-1,2,3,5-tetraphenyl-1-pyrimidinium-6-olate (25a): Into a 10 mL round-bottomed flask, 5 mL of acetone was added and sequential addition of the following reactants was made under stirring at room temperature: 0.677 g (10^{-3} mol) of dipentachlorophenyl phenylmalonate **16** and 0.272 g (10^{-3} mol) of N,N'-diphenylbenzamidine **4a**. To the milky suspension obtained, 0.202 g (2×10^{-3} mol) of triethylamine was added. Within 1 min after the latter addition, a yellow solid precipitated at the bottom of the flask, leaving a yellow solution. The whole system was then stirred for 24 h at room temperature. Afterwards, the yellow precipitate was filtered off and recrystallized from chlorobenzene, yielding betaine **25a** as yellow bright crystals. Results are given in Table-6.

Synthesis of pyrimidinic betaines with fatty chain 25b-f[15]: The same experimental protocol as for the synthesis of compound **25a** was applied for the synthesis of **25b-f**, using N,N'-diphenylalkamidines **4b-f** instead of N,N'-diphenylbenzamidine **4a**. Identical work-up was employed for the isolation of **25b-f**. The recrystallization of these products from acetone afforded powdery white solids. Results are given in Table-6.

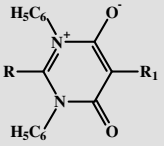
IR, UV and NMR spectral results of **24** and **25a-f** are compiled in Tables 7-10. For IR spectra, KBr pellets were used for **24** and **25a** and nujol for **25b-f**.

Mass spectroscopy results for **25a** confirmed its molecular formula $C_{28}H_{20}O_2$; M + 1 peak appeared at 417.

RESULTS AND DISCUSSION

Synthesis of N,N'-diphenylalkamidines: Alkanilides **3b-f**, starting materials for N,N'-diphenylalkamidines **4b-f**, were realized by a procedure described in the literature for benzanilide synthesis **3a**[8]. As shown in **Scheme-I**, the reaction of fatty acid **2b-f** with an excess of aniline at a temperature of as high as 160-200 ºC afforded the corresponding alkanilides in form of white solids. As presented in Table-1, the yields were moderate to high, 73-96 %. Also, their melting points showed an increasing trend with alkyl group. However, they were half

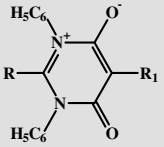
TABLE-6
YIELDS AND PHYSICAL PROPERTIES OF THE DIFFERENT BETAINES



Betaine	R	R_1	Aspect	Yield (%)	m.p. (ºC) [lit.]
24	Phenyl	H	White solid[a]	41**	265-266; 255-257[a] [20b]
25a	Phenyl	Phenyl	Yellow solid[a]	49***	291-293[a]; 293 [22]
25a	Phenyl	Phenyl	Yellow crystal[a*]	25	303-305[a]
25b	$CH_3(CH_2)_8$–	Phenyl	White solid[a]	20	–
25c	$CH_3(CH_2)_{10}$–	Phenyl	″	32	171.5[a]
25d	$CH_3(CH_2)_{12}$–	Phenyl	″	31	191.5[a]
25e	$CH_3(CH_2)_{14}$–	Phenyl	″	30	196[a]
25f	$CH_3(CH_2)_{16}$–	Phenyl	″	35	176[a]

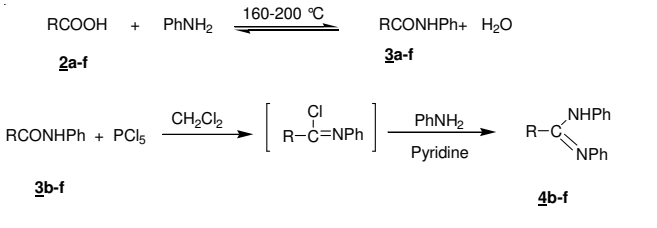
a:decomposes, *Chlorobenzene was employed as a recrystallizing solvent. **76 % [20b]. ***89 % [22].

TABLE-7
IR RESULTS OF THE DIFFERENT BETAINES



Betaine[†]	R	R_1	Characteristic bands (cm^{-1})		[Literature]
24	Phenyl	H	1718, 1678	(C=O)	1700, 1665
			2980	(C-H)	3060-3040 [20b]
			1620	(C=C) (aromatics)	
25a	Phenyl	Phenyl	1680, 1650	(C=O)**	1680, 1660-1630
			1595	(C=C) (aromatics)	1590 [22]
25b	$CH_3(CH_2)_8$–	Phenyl	1672*, 1626	C=O	
			1592	C=C) (aromatics)	–
25c	$CH_3(CH_2)_{10}$–	Phenyl	1673*, 1628	(C=O)	
			1590	(C=C) (aromatics)	–
25e	$CH_3(CH_2)_{14}$–	Phenyl	1673*, 1630	(C=O)	
			1550	(C=C) (aromatics)	–
25f	$CH_3(CH_2)_{16}$–	Phenyl	1670*, 1630	(C=O)	
			1588	(C=C) (aromatics)	–

*As shoulder. **Overlapped bands (C=C) and (C=N). [†]**25d** had the same characteristic bands as **25b,c,e,f**.



a, R = Ph; **b**, R = C_9H_{19}; **c**, R = $C_{11}H_{23}$; **d**, R = $C_{13}H_{27}$; **e**, R = $C_{15}H_{31}$; **f**, R = $C_{17}H_{35}$

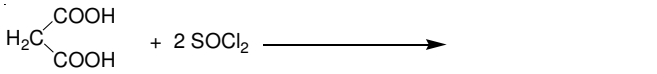
Scheme-I

that of benzanilide **3a** (163 ºC). These findings are in a good agreement with those reported elsewhere[12a,13]. The results of different spectral analyses indicated the success of the reaction and the desired products were indeed obtained. IR spectra revealed a band at 1655 cm^{-1}, assigned to carbonyl group of the amide function and the UV spectra showed a band at λ_{max} at 241 nm, assigned to $\pi \rightarrow \pi^*$ transition.

Application of the experimental protocol reported by Hontz and Wagner[9b] for the synthesis of **4b-f**, failed to give the desired products as revealed by TLC analysis. In all cases, a black residue was ensued at a temperature of 160 ºC, resulting from a plausible degradation of the products. Therefore, mild conditions were adopted for their preparation; as shown in **Scheme-I**. The alkanilides reacted first with phosphorous pentachloride in dried dichloromethane at room temperature for 2 h. The intermediate product was then allowed to react with aniline in the presence of pyridine. The N,N'-diphenyl-alkamidines were isolated as white solids in low to moderate yields, 52-73 % (Table-2). The melting points of N,N'-diphenyl-alkamidines were in the range of 91-98 ºC, higher than those of their starting alkanilides and followed an increasing trend with the fatty group length as found with the set of alkanilides. It was found that the yields were nearly the same when the reactions were performed under reflux at 40 ºC.

Synthesis of malonate derivatives: For the synthesis of malonate derivatives, conventional esters such as ethyl alkylmalonates used by Tschitchibabin[14] for preparing bicyclic betaines were precluded because extreme conditions were required. Instead, two more reactive malonic acid derivatives, namely malonyl chloride and dipentachlorophenyl phenyl-malonate were made by different procedures. For the former,

a classical method[10] was employed, involving the reaction of malonic acid with thionyl chloride, eqn. 2.



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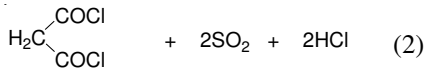
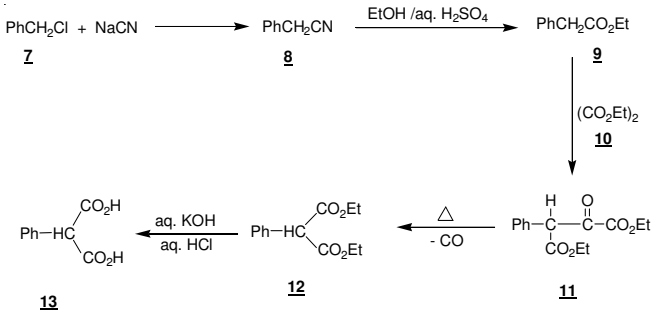


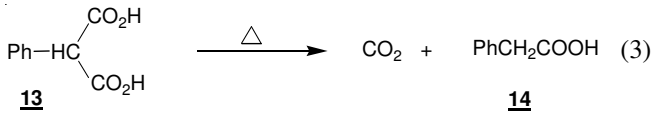
6 (2)

Dipentachlorophenyl phenylmalonate was obtained by esterification of phenyl malonic chloride with dipentachlorophenol, **Scheme-III**. As to phenyl malonic acid, a multistep synthesis was conceived starting from benzyl chloride as traced in **Scheme-II**. Treatment of benzyl chloride with sodium cyanide led to phenyl acetonitrile, which was converted into ethyl phenylacetate upon reaction with ethanol in the presence of sulfuric acid. Using sodium ethylate as a base, the ethyl phenylacetate underwent Claisen condensation with ethyl oxalate to yield 2-oxo-3-phenylbutanedioic acid ethyl diester as a clear oil, which was thermally decarbonylated (170-180 ºC (under reduced pressure)) to end up with ethyl phenylmalonate in a poor yield, 3.6 %.



Scheme-II

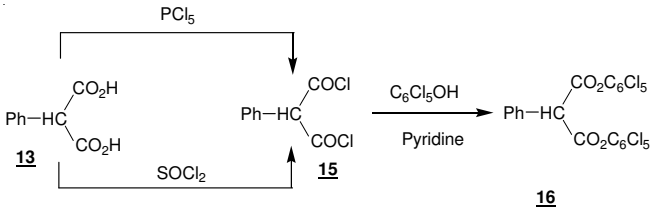
This actual yield was enhanced to about 61 % by prolonging the time of decarbonylation process to 12 h. The ester was then hydrolyzed to obtain phenylmalonic acid. The latter was very sensitive to heat, that is, upon its distillation, a decarboxylation occurred to give phenylacetic acid (eqn. 3).



13 14 (3)

Lowering the temperature at 51-73 ºC, extending the time (overnight) of the reaction of hydrolysis of ethyl phenylmalonate and deleting the distillation step, gave phenylmalonic acid as a white solid with a m.p. of 150-152 ºC (153-155 ºC[27]).

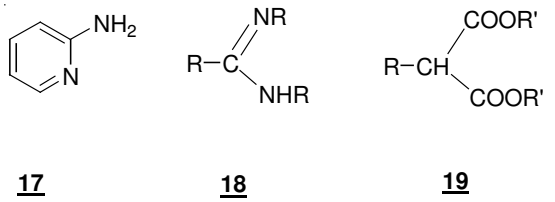
According to the method as described in[11] and as shown in **Scheme-III**, dipentachlorophenyl phenylmalonate was obtained in a quantitative yield (92 %). It turned out that, in present case, the yield did not exceed 10 %, even after several attempts. However, modification of the reaction conditions as delineated in the experimental procedure, afforded improved yields, 56 and 82 % in cases of thionyl chloride and phosphorous pentachloride, respectively. For the success of this reaction, not only should it work out under the modified conditions, but also the reactants must be anhydrous.



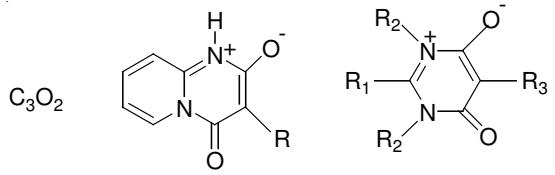
Scheme-III

Dipentachlorophenyl phenylmalonate was isolated in form of white solid with a m.p. of 226-230 ºC. The physical properties and spectral analyses of this ester were in accord with the literature[11]. Table-3 presents the physical properties and yields of the malonic acid derivatives, involved in **Schemes II** and **III**.

Synthesis of pyrimidine-bearing betaines: Betaines having pyrimidine moiety have attracted the interest of many authors, for their peculiar structure[17], their biological activity[17,18], their proneness to cycloaddition reaction[19,20] and their chemical stability[21]. As to their preparation, those with bicyclic and monocyclic structures **21** and **22**, were made *via* condensation of α-aminopyridine **17** or the amidine **18** with the appropriate malonic acid derivatives **19**[14] or with the carbon suboxide **20**[20]. In present work, some of these methods were applied to make pyrimidine-containing betaines.



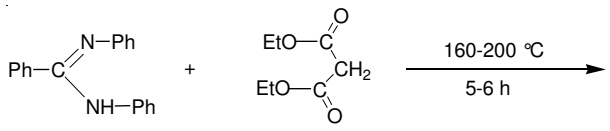
17 18 19



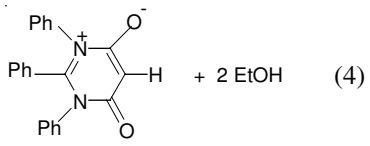
20 21 22

Synthesis of 4*H*-4-oxo-1,2,3-triphenyl-1-pyrimidinum-6-olate (24): We evaluated the experimental protocol described by Tschitschibabin[14] in making betaine **24**, by condensing N,N'-diphenylbenzamidine **4a** instead of α-aminopyridine **17**, with ethyl malonate **23**, as depicted in eqn. 4. Because of the reduced chemical reactivity of the latter ester, extreme conditions were employed, that is, heating the mixture at temperature of 160-200 ºC for 5-6 h. The isolated white solid was characterized spectroscopically and the results resembled with the structure of the betaine **24** and agreed with those reported by Potts and Sorm[20b] for the product of the condensation of the same amidine with carbon suboxide. The yield was 41 % (Table-6), lower than the reported one, 76 %[20b]. The melting

point of synthesized present betaine was found to be higher, 265 ºC against 255 ºC[20b].



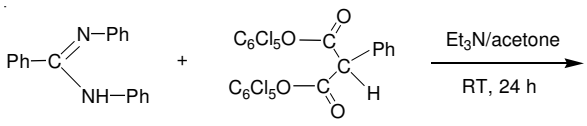
4a **23**



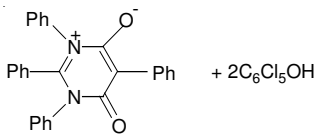
(4)

24

Synthesis of 4*H*-4-oxo-1,2,3,5-tetraphenyl-1-pyrimidinum-6-olate (25a): Substituting dipentachlorophenyl phenylmalonate **16**, a more reactive ester, for the commercially available ethyl malonate **23**, was inspired by the reaction, making bicyclic betaines. In this reaction (eqn. 5), N,N'-diphenylbenzamidine **4a** was employed instead of α-aminopyridine **17**. The reaction was run at room temperature for 24 h. As confirmed by TLC analysis, monocyclic betaines required longer time (24 h) than the bicylic analogues. The yellow solid betaine **25a**, being insoluble in the reaction medium, precipitated as soon as formed. Again, the yield (Table-6) of present betaine was much lower than the one reported by Kappe and Lube[22], 49 against 89 %. The latter authors carried out the condensation of the same amidine with 2,4,6-trichlorophenyl phenylmalonate at a temperature of 110 ºC and a time of 10 min. However, the betaine, recrystallized in chlorobenzene, had a melting point 303-305 ºC, a value higher than the one reported by these authors, 293 ºC, suggesting that their betaine was not purified. The different spectroscopy analyses confirmed the real structure of the betaine.



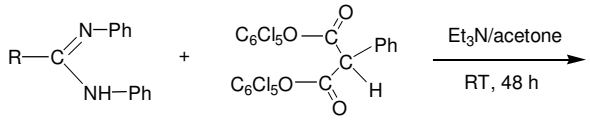
4a **16**



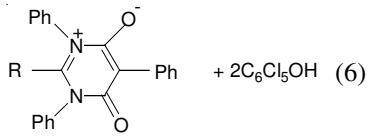
(5)

25a

Synthesis of betaines with fatty alkyl chain: Attempts of condensing ethyl malonate and malonyl chloride with the fatty amidines failed. However, the condensations of dipentachlorophenyl phenylmalonate **16** with the mentioned amidines **4b-f** were successful. The reactions (eqn. 6) were carried under reaction conditions identical to those of eqn. 5, with the exception of reaction time which was extended to 48 h. White products precipitated from the reaction mixtures as soon as they were formed. The different betaines **25b-f** were isolated in low yields, 20-35 % as shown in Table-6. Their melting points ranged from 171-196 ºC and there was no general trend of this physical property with increasing alkyl chain length. Their spectral characterizations are compiled in Tables 7-10.



4a **16**



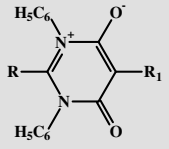
(6)

25a

R = **a**, Ph; **b**, C_9H_{19}; **c**, $C_{11}H_{23}$; **d**, $C_{13}H_{31}$; **f**, $C_{17}H_{35}$

Biological assays: Biological activity of the betaines **25a-f** was assessed against gram-positive and gram-negative target germs as well fungus and yeasts. The preliminary results showed that these betaines showed a positive antibacterial activity against gram-negative bacteria *Salmonella enterica*. An antifungal activity against the fungi *Mucor ramannianus* and biological activity against *Candida albicans* yeast were

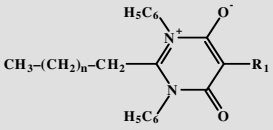
TABLE-8
UV RESULTS OF THE DIFFERENT BETAINES



Betaine†	R	R_1	λ_{max} (nm) (ε)	[Literature]
24[2]	Phenyl	H	213 (25120), 254.1 (25560), 319 (8680), 330 (8880)	215(41686.8), 253, (9120.1), 235(17782,7), 270-350 ** [20b]
25a[1]	Phenyl	Phenyl	215(33200), 260*, 325 (4400)	–
25b[2]	$CH_3(CH_2)_8$–	Phenyl	216(15688.2), 228(7893.8), 280-306**	–
25c[2]	$CH_3(CH_2)_{10}$–	Phenyl	218(16152.6), 228(7860.7), 275-308**	–
25e[2]	$CH_3(CH_2)_{14}$–	Phenyl	218(15920.4), 228(10248.7), 278-310**	–
25f[2]	$CH_3(CH_2)_{16}$–	Phenyl	218.21635.6), 228.2(10281.9), 280-310**	–

*As shoulder. **Plateau. [1]Ethanol as solvent. [2]Methanol as solvent. †**25d** had the same characteristic bands as **25b,c,e,f**.

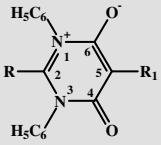
TABLE-9
^{1}H NMR CHARACTERISTIC PEAKS OF THE BETAINES, **24, 25a** AND **25f**



Betaine	R_1	Solvent	Proton chemical shifts δ (ppm)				
			Aromatic H	H-5	H (α CH_2)	H ($(CH_2)_n$)	H (CH_3)
24	H	DMSO-d_6	7.58 (6.87-7.5)*	4.20 (4.99)*	–	–	–
25a	Phenyl	DMSO-d_6	6.9-7.8	–	–	–	–
25f	Phenyl	$CDCl_3$	7.23	–	2.38	1.27	0.89

*Ref. [20b].

TABLE-10
^{13}C NMR CHARACTERISTIC PEAKS OF THE BETAINES, **24** AND **25a**



Betaine†	R	R_1	Carbon chemical shifts δ (ppm)			
			C-2	C-4	C-5	C-6
24	Phenyl	H	153.33 (157)*	151.12 (156)*	80.95 (81)*	151.12 (156)*
25a	Phenyl	Phenyl	158.9-159.4	158.9-159.4	158.9-159.4	158.9-159.4

*Ref. [28]. †Other betaines were not analyzed by ^{13}C NMR.

observed. These activities were found to increase with increasing betaine concentration.

Conclusion

Modifications of the reported procedures allowed the preparations of a set of N,N'-diphenylalkamidines and a set of pyrimidine-bearing betaines with fatty alkyl chain. N,N' Diphenylalkamidines could be formed by simply stirring the mixtures specified in the experimental section, in dichloromethane at room temperature. Dipentachlorophenyl phenylmalonate was realized *via* a multistep synthesis, starting from benzyl chloride. Betaines with pyrimidine entity were preferentially made using a more reactive diester, namely dipentachlorophenyl phenylmalonate. Reaction conditions for making these betaines were found, that is, room temperature and longer reaction times. Yet, our on-going research is being focused on setting the appropriate conditions to enhance the actual yields. Preliminary biological tests revealed that the betaines possessed antibacterial and antifungal activities and activity against yeasts.

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