Synthesis of Pyrimidine, Thiazolopyrimidine, Pyrimidotriazine and Triazolopyrimidine Derivatives and their Biological Evaluation

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Thiazolopyrimidines, Pyrimidotriazines, 2-Pyrazolopyrimidines, Triazolopyrimidines, Ethyl Benzoylacetate, Pyrimidin-4-one-2-thione

Pyrimidin-4-one-2-thione (**3**) was synthesized *via* the reaction of thiourea (**1**) with ethyl benzoylacetate (**2**) and was taken as a starting material for the present study *via* its reactions with the halogen-containing reagents **6**a-d and **10**a-c to give the corresponding thiazolopyrimidines **8**, **9** and **12a-c**. The 2-hydrazino derivatives **5** were synthesized either *via* the reaction of **3** or **4** with hydrazine hydrate. Compound **5** reacted with **6a-c** and **10a-c** to give the corresponding pyrimidotriazines **17a-c** and **19** respectively. Also, compound **5** reacted with the active methylene-containing reagents **13** and **2a,b** to give the corresponding 2-pyrazolopyrimidines **15** and **22a,b** respectively. On the other hand, the triazolopyrimidines **21a,b** and **30a,b** were also obtained *via* the reaction of **5** with each of formic acid, acetic anhydride, ethyl chloroformate and carbon disulfide respectively. Some of the newly synthesized heterocyclic derivatives were tested for their biological activity.

Introduction

Although a number of publications [1–4] have been appeared concerning the synthesis of pyrimidine derivatives, no approach using ethyl benzoylacetate (**2a**) and thiourea (**1**) as the starting materials has been reported. We now wish to report a convenient and simple synthesis for **3** *via* the reaction of thiourea (**1**) with ethyl benzoylacetate (**2a**) in ethanolic sodium acetate. Structure of **3** was established based on, both, spectral and analytical data (*cf.* Tables I and II). Moreover, its mass spectrum gave *m/z*=204, corresponding to the molecular weight of a molecular formula $C_{10}H_8N_2SO$ of the assigned structure (*cf.* Chart 1). In continuation to our previous work [5] and due to the reported biological activity [6–9] we were stimulated to synthesize more derivatives of this ring system. Compounds **3** and **5** were taken as the reactive starting materials for the present study, owing to the presence of more than one active site in both of them.

Results and Discussion

It has been found that compound **3** reacted with chloroacetic acid (**6a**) in ethanolic sodium ethoxide to give a product corresponding to dehydrochlorination. The IR of such product showed bands of (C=O) and OH of the carboxyl group in addition to the functional groups present in the starting material. Its ^{1}H NMR revealed signals of $-COOH$ and $-CH_2$-S- protons in addition to the signals originally present in the starting material (*cf.* Table II). By considering such results in addition to elemental analyses data, compound **7a** could be formulated as 6-phenyl-2-S-carboxymethylpyrimidine-4-one. A good evidence for structure **7a** was given through its cyclization in ethanolic hydrochloric acid to afford 4-phenylthiazolo[3,2-a]pyrimidine-2,5-dione **8**. The structure of **7a**, and hence of **8**, was confirmed, based on IR, ^{1}H NMR and elemental analyses (*cf.* Tables I and II). Moreover, their mass spectra gave *m/z*=262 and 244, respectively which corresponded to the molecular weights of the molecular formulas $C_{12}H_{10}N_2SO_3$ and $C_{12}H_8N_2SO_2$ of the assigned structures (*cf.* Chart 1).

In a similar manner, compound **3** reacted with ethyl chloroacetate and chloroacetamide **6b,c** to afford the products **7b,c** whose structures were established, based on IR, ^{1}H NMR and elemental analyses (*cf.* Tables I and II). Similar to the behavior of **7a**, **7b,c** were cyclized under the same experimental conditions to afford products *via* elimination of ethanol and ammonia in a respective

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Table I. Physical and analytical data of the compound prepared.

Comp.	M.p. (°C)	Yield (%)	Molecular formula	Analysis Calcd/Found (%) C	H	N	S
3	266	87	$C_{10}H_8N_2SO$	58.82	3.92	13.73	15.69
				58.6	4.2	14.0	15.4
4	246	81	$C_{11}H_{10}N_2SO$	60.55	4.58	12.84	14.67
				60.7	4.4	13.0	14.4
5	226	76	$C_{10}H_{10}N_4O$	59.41	4.95	27.72	–
				59.2	5.2	27.5	–
7a	218	66	$C_{12}H_{10}N_2SO_3$	54.96	3.82	10.69	12.21
				55.1	4.0	10.9	12.5
7b	225	59	$C_{14}H_{14}N_2SO_3$	57.93	4.83	9.66	11.03
				58.2	5.0	9.8	11.2
7c	235	64	$C_{12}H_{11}N_3SO_2$	55.17	4.21	16.09	12.26
				54.9	4.3	15.9	12.4
7d	210	77	$C_{18}H_{14}N_2SO_2$	67.08	4.35	8.70	9.94
				67.2	4.3	8.5	10.2
8	280	89	$C_{12}H_8N_2SO_2$	59.02	3.28	11.48	13.11
				60.2	3.5	11.2	13.4
9	270	60	$C_{18}H_{12}N_2SO$	71.01	3.95	9.21	10.53
				71.2	4.1	9.4	10.3
11a	222	58	$C_{13}H_{12}N_2SO_2$	60.00	4.62	10.77	12.31
				60.2	4.4	10.9	12.5
11b	214	77	$C_{15}H_{14}N_2SO_3$	59.60	4.63	9.27	10.59
				59.8	4.8	9.0	10.7
11c	206	80	$C_{16}H_{16}N_2SO_4$	57.83	4.81	8.43	9.63
				57.6	5.0	8.2	9.7
12a	275	75	$C_{13}H_{10}N_2SO$	64.46	4.13	11.57	13.22
				64.2	3.9	11.3	13.4
12b	268	96	$C_{15}H_{12}N_2SO_2$	63.38	4.22	9.85	11.26
				63.1	4.5	10.1	11.5
12c	276	88	$C_{16}H_{14}N_2SO_3$	61.14	4.45	8.91	10.19
				61.4	4.2	9.2	10.3
15	150	87	$C_{15}H_{14}N_4O$	67.66	5.26	21.05	–
				67.8	5.4	21.2	–
16a	270	68	$C_{13}H_{14}N_4O_2$	60.46	5.42	21.70	–
				60.2	5.6	21.9	–
16b	210	87	$C_{15}H_{16}N_4O_3$	60.00	5.33	18.66	–
				59.8	5.6	18.4	–
16c	245	68	$C_{16}H_{18}N_4O_4$	58.18	5.45	16.96	–
				58.3	5.6	17.2	–
17a	312	77	$C_{13}H_{12}N_4O$	65.00	5.00	23.33	–
				64.8	5.3	23.5	–
17b	273	82	$C_{15}H_{14}N_4O_2$	63.82	4.96	19.85	–
				64.1	4.7	20.0	–
17c	298	88	$C_{16}H_{16}N_4O_3$	61.53	5.12	17.94	–
				61.3	5.4	18.1	–
18a	240	76	$C_{12}H_{12}N_4O_3$	55.38	4.61	21.53	–
				55.5	4.8	21.7	–
18b	208	66	$C_{14}H_{16}N_4O_3$	58.33	5.55	19.44	–
				58.5	5.8	19.6	–
18c	254	65	$C_{12}H_{13}N_5O_2$	55.59	5.01	27.02	–
				55.8	5.3	27.2	–
19	275	83	$C_{12}H_{10}N_4O_2$	59.50	4.13	23.14	–
				59.7	4.3	23.3	–
21a	295	88	$C_{11}H_8N_4O$	62.26	3.77	26.41	–
				62.5	4.0	26.2	–
21b	129	87	$C_{12}H_{10}N_4O$	63.71	4.42	24.77	–
				63.5	4.6	25.0	–
22a	264	91	$C_{19}H_{14}N_4O_2$	69.09	4.24	16.96	–
				69.2	4.5	17.2	–
22b	274	74	$C_{14}H_{12}N_4O_2$	62.68	4.47	20.89	–
				62.9	4.6	21.1	–

Table I. (continued).

Comp.	M.p. (°C)	Yield (%)	Molecular formula	Analysis Calcd/Found (%) C	H	N	S
25	>300	76	$C_{13}H_{11}N_5O_2$	57.99	4.08	26.02	–
				58.2	4.3	26.2	–
27a	272	88	$C_{17}H_{14}N_4O$	70.34	4.82	19.31	–
				70.1	5.0	19.1	–
27b	295	80	$C_{17}H_{13}N_4OCl$	62.86	4.00	17.25	–
				63.0	4.2	17.5	–
27c	>300	86	$C_{15}H_{12}N_4SO$	60.81	4.05	18.91	10.81
				61.0	4.2	19.1	11.0
30a	260	76	$C_{11}H_8N_4O_2$	57.89	3.50	24.56	–
				58.1	3.7	24.7	–
30b	124	69	$C_{11}H_8N_4SO$	54.09	3.27	22.95	13.11
				54.2	3.5	23.2	13.4

% of Cl for compound **27b** Calcd/Found is 10.93/11.2.
All compounds are crystallized from ethanol except for compounds **15**, **21**b, **25** and **27**a-c, which are crystallized from acetic acid.

manner. The mass spectra of **7b,c** gave *m/z*=290 and 261, respectively which corresponded to the molecular weights of the molecular formulas $C_{14}H_{14}N_2SO_3$ and $C_{12}H_{11}N_3SO_2$ of the assigned structures (*cf.* Chart 1). It is remarkable to report here that the cyclization product of the **7a-c** was similar in all aspects (m.p., mixed m. p., IR, ^{1}H NMR and mass spectra).

On the other hand, compound **3** reacted with ω-bromoacetophenone **6d** in ethanolic sodium ethoxide to afford the corresponding 6-phenyl-2-S-benzoylmethylpyrimidine-4-one (**7d**) *via* dehydrobromination. Compound **7**d was cyclized in ethanolic hydrochloric acid to afford 4,5-diphenylthiazolo[3,2-a]pyrimidine-2-one **9**. The structures **7d** and **9** were confirmed depending on the data of, both, spectral and elemental analyses (*cf.* Tables I and II). Moreover, their mass spectra gave *m/z*= 322 and 304 respectively which corresponded to the molecular weights of the molecular formulas $C_{18}H_{14}N_2SO_2$ and $C_{18}H_{12}N_2SO$ of the assigned structure (*cf.* Chart 1). The *m/z* values of **7a-d** were 262, 290, 261 and 322, while those of their cyclization products **8** and **9** were 244 and 304. This proved that **7a-c** cyclized *via* elimination of water, ethanol and ammonia, respectively, to give the cyclization product **8** while **7d** cyclized *via* dehydration to give the cyclization product **9**.

The synthon **3** reacted also with chloroacetone (**10a**), α-chloroacetylacetone (**10b**) and ethyl α-chloroacetoacetate (**10c**) under similar experimental conditions to afford the corresponding 2-S-alkyl pyrimidinone derivative **11a-c**, respectively, *via* dehydrochlorination in each case. The structures of **11a-c** were established, based on IR, ^{1}H NMR and elemental analyses data (*cf.* Tables I and II). A good evidence for structures **11a-c** arose from their cyclization in ethanolic hydrochloric acid, to afford the corresponding thiazolo[3,2-a]pyrimidines **12a-c**, respectively. The above mentioned cyclization reactions most probably proceeded through dehydration of **11a-c**. This results arose from the mass spectra of **11a-c** which gave *m/z*= 260, 302 and 332, while that of **12a-c** gave *m/z*= 242, 284 and 314 which proved elimination of a water molecule in each case (*cf.* Chart 1).

The synthetic potentiality of **3** was investigated further through its reaction with methyl iodide to give the corresponding 6-phenyl-2-S-methylpyrimidine-4-one (**4**). Compound **4** reacted with hydrazine hydrate to give the sulfur-free product **5**. The structures of, both, **4** and **5** were established based on IR, ^{1}H NMR and elemental analyses (*cf.* Tables I and II). A good elucidation of structure **5** was given through its preparation *via* another route. Thus, compound **3** reacted with hydrazine hydrate to give the same sulfur-free product **5**, found identical in all aspects (m.p., mixed m. p., IR, ^{1}H NMR and elemental analyses) with that given from the reaction of **4** with hydrazine hydrate. Compound **5** was formulated as 2-hydrazino-6-phenylpyrimidine-4-one by considering its mass spectrum (*m/z*= 202) which corresponds to the molecular formula $C_{10}H_{10}N_4O$ of the assigned

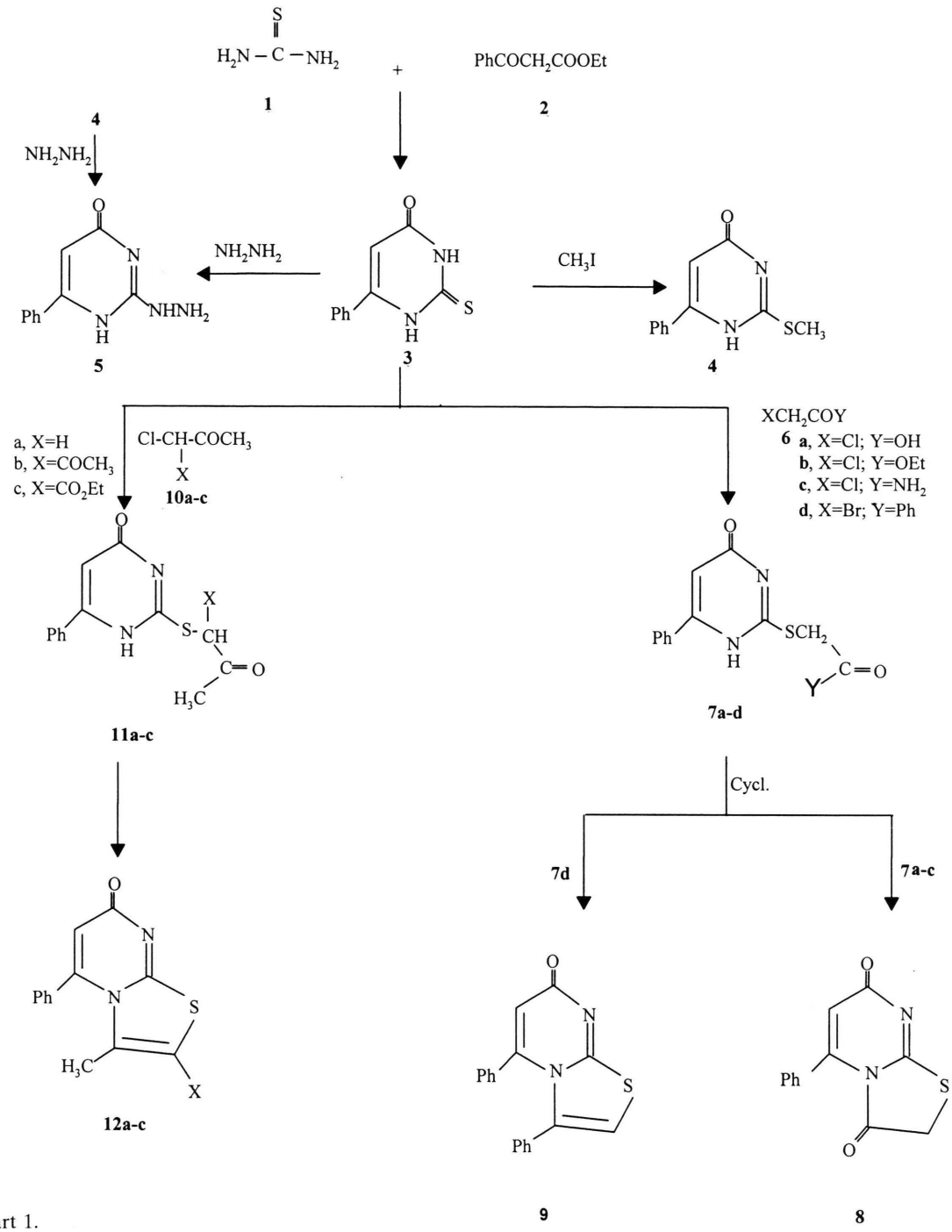

Chart 1.

structure (*cf.* Chart 1). Compound **5** was taken as another synthon in the present study owing to the presence of more than one active site. Thus, it has been found that compound **5** reacted with acetylacetone (**13**) in ethanol containing the catalytic amount of triethylamine to afford the corres-

Table II. Spectroscopic data of the newly synthesized compounds.

Comp.	IR (cm^{-1})	^1H NMR (δppm)
3	3192(NH); 3076 (aromatic CH); 1678(C=O); 1603(C=C) and 1564(C=S).	3.7(s, 1H, pyrimidine H-5); 7.0–7.9(m, 5H, ArH's) and 11.6(s, br., 2H, NH).
4	3187(NH); 3069(aromatic CH); 2879(sat. CH); 1690(C=O); 1600(C=C) and 1558(C=S).	2.3(s, 3H, SCH_3); 3.5(s, 1H, pyrimidine H-5); 5.2(s, br., 1H, NH) and 7.0–7.9(m, 5H, ArH's).
5	3379, 3297, 3278, 3189(NH_2 and NH); 3082(aromatic CH); 1691(C=O); 1614(C=N) and 1600(C=C).	3.4(s, 1H, pyrimidine H-5); 5.0(s, br., 1H, NH pyrimidine); 6.1(s, br., 1H, NH hydrazide); 7.0–8.1(m, 5H, ArH's) and 9.3(s, br., 2H, NH_2 hydrazide).
7a	3400–2400(H-bonded OH); 1712(C=O acid); 1691(C=O ring); 1613(C=N) and 1600(C=C).	3.1(s, 1H, pyrimidine H-5); 3.9(s, 2H, -SCH_2-); 5.3(s, br., 1H, NH pyrimidine); 6.9–7.8(m, 5H, ArH's) and 10.9(s, br., 1H, COOH).
7b	3180(NH); 3069(aromatic CH); 2987(sat. CH); 1739(C=O ester); 1691(C=O ring); 1617(C=N) and 1605(C=C).	1.0(t, 3H, CH_3CH_2-); 2.9(s, 1H, pyrimidine H-5); 3.7(s, 2H, -SCH_2-); 4.0(q, 2H, CH_3CH_2-); 5.2(s, br., 1H, NH pyrimidine); and 7.0–7.9(m, 5H, ArH's).
7c	3336, 3278, 3195(NH_2 and NH); 3076(aromatic CH); 2979(sat. CH); 1697(C=O); and 1605(C=C).	3.1(s, 1H, pyrimidine H-5); 3.8(s, 2H, -SCH_2-); 5.1(s, br., 1H, NH pyrimidine); 6.0(s, br., 2H, NH_2) and 7.0–8.1(m, 5H, ArH's).
7d	3187(NH); 3075(aromatic CH); 2977(sat. CH); 1709(C=O ketone); 1695(C=O ring); and 1605(C=C).	3.0(s, 1H, pyrimidine H-5); 3.9(s, 2H, -SCH_2-); 5.4(s, br., 1H, NH pyrimidine); and 7.0–8.0(m, 5H, ArH's).
8	3083(aromatic CH); 2982(sat. CH); 1688(C=O); and 1605(C=C).	2.8(s, 1H, pyrimidine H-5); 4.1(s, 2H, -CH_2- thiazole ring) and 7.0–7.9(m, 5H, ArH's).
9	3079(aromatic CH); 1700(C=O); 1613(C=N) and 1602(C=C).	3.1(s, 1H, pyrimidine H-5); 4.6(s, 1H, -CH=) and 7.0–8.1(m, 10H, ArH's).
11a	3179(NH); 3078(aromatic CH); 2978(sat. CH); 1710 (C=O); 1610(C=N) and 1600(C=C).	2.2(s, 3H, -$COCH_3$); 3.1(s, 1H, pyrimidine H-5); 3.9(s, 2H, -SCH_2CO-); 5.3(s, br., 1H, NH) and 7.1–7.8(m, 5H, ArH's).
11b	3182(NH); 3075(aromatic CH); 2977(sat. CH); 1690 (C=O); 1612(C=N) and 1600(C=C).	2.0(s, 6H, two -$COCH_3$); 3.3(s, 1H, pyrimidine H-5); 4.1(s, H, -SCH); 5.3(s, br., 1H, NH) and 7.0–8.1(m, 5H, ArH's).
11c	3197(NH); 3083 aromatic CH); 2979(sat. CH); 1732(C=O ester); 1708(C=O ketone); 1687 (C=O ring); 1615(C=N) and 1600(C=C).	1.1(t, 3H, CH_3CH_2-); 1.9(s, 3H, -$COCH_3$); 2.8(s, 1H, pyrimidine H-5); 3.4(q, 2H, CH_3CH_2-); 4.1(s, H, -SCH); 5.1(s, br., 1H, NH) and 7.0–8.1(m, 5H, ArH's).
12a	3069 aromatic CH); 2976(sat. CH); 1689 (C=O ring); 1611(C=N) and 1600(C=C).	1.1(t, 3H, CH_3); 3.0(s, 1H, pyrimidine H-5); 4.5(s, H, =CH-) and 7.1–7.9(m, 5H, ArH's).
12b	3072 aromatic CH); 2977(sat. CH); 1715(C=O ketone); 1687 (C=O ring); 1610(C=N) and 1601(C=C).	1.0(t, 3H, CH_3); 2.1(s, 3H, $COCH_3$); 3.2(s, 1H, pyrimidine H-5) and 7.0–7.8(m, 5H, ArH's).
12c	3079 aromatic CH); 2989(sat. CH); 1738(C=O ester); 1690 (C=O ring); 1616(C=N) and 1600(C=C).	0.9(t, 3H, CH_3); 1.1(t, 3H, CH_3CH_2-); 3.0(s, 1H, pyrimidine H-5); 3.5(q, 2H, CH_3CH_2-) and 6.9–8.2(m, 5H, ArH's).
15	3192(NH); 3083 aromatic CH); 2976(sat. CH); 1690 (C=O ring); 1616(C=N) and 1603(C=C).	1.3(s, 6H, two CH_3); 2.9(s, 1H, pyrimidine H-5); 3.4(s, 1H, pyrazole); 5.4(s, br., NH) and 7.0–7.9(m, 5H, ArH's).
16a	3222, 3190, 3168(NH); 3075 aromatic CH); 2988(sat. CH); 1711(C=O ketone); 1673 (C=O ring); 1611(C=N) and 1601(C=C).	1.7(s, 3H, $COCH_3$); 2.1(s, 2H, -$COCH_2$-); 3.3(s, 1H, pyrimidine H-5); 4.9(s, br., three NH) and 7.0–7.8(m, 5H, ArH's).
16b	3220, 3202, 3187(NH); 3077 aromatic CH); 2979 (sat. CH); 1687 (C=O) ; 1615(C=N) and 1600(C=C).	2.0(s, 6H, two $COCH_3$); 2.3(s, 1H, -CH-); 3.1(s, 1H, pyrimidine H-5); 5.2(s, br., three NH) and 7.0–7.8(m, 5H, ArH's).
16c	3231, 3217, 3193(NH); 3080 aromatic CH); 2978 (sat. CH); 1730(ester C=O); 1679 (ring C=O) ; 1610 (C=N) and 1600(C=C).	1.0(t, 3H, CH_3CH_2-); 2.1(s, 3H, $COCH_3$); 2.4(s, 1H, -CH-); 3.0(s, 1H, pyrimidine H-5); 3.5(q, 2H, CH_3CH_2-); 5.1(s, br., three NH) and 7.0–8.1(m, 5H, ArH's).
17a	3223, 3189(NH); 3069 aromatic CH); 2978 (sat. CH); 1688 (ring C=O) ; 1617(C=N) and 1602(C=C).	1.2(s, 3H, CH_3); 3.1(s, 1H, pyrimidine H-5); 5.0(s, 1H, triazine H-3); 6.4(s, br., 2H, two NH) and 7.1–8.2(m, 5H, ArH's).

Table II. (continued)

Comp.	IR (cm^{-1})	^1H NMR (δppm)
17b	3200, 3195(NH); 3079 aromatic CH); 2975 (sat. CH); 1717(ketone C=O); 1692(C=O ring); 1612 (C=N) and 1600(C=C).	1.0(s, 3H, CH_3); 1.9(s, 3H, $COCH_3$); 3.2(s, 1H, pyrimidine H-5); 6.1(s, br., 2H, two NH) and 7.0–7.9(m, 5H, ArH's).
17c	3217, 3195(NH); 3078 aromatic CH); 2977 (sat. CH); 1737(ketone C=O); 1694(C=O ring); 1613 (C=N) and 1603(C=C).	1.0(s, 3H, CH_3); 1.3(t, 3H, CH_3CH_2-); 3.1(s, 1H, pyrimidine H-5); 3.5(q, 2H, CH_3CH_2-); 5.9(s, br., 2H, two NH) and 6.9–7.8(m, 5H, ArH's).
18a	3400–2397(H-bonded OH); 1708(acid C=O); 1678(C=O ring); 1611 (C=N) and 1601(C=C).	1.9(s, 2H, -$COCH_2$-); 3.2(s, 1H, pyrimidine H-5); 5.4(s, br., 3H, three NH); 7.0–7.9(m, 5H, ArH's) and 11.1(s, br., 1H, COOH).
18b	3320, 3276, 3193(NH); 3072(aromatic CH); 2978(sat., CH); 1732(ester C=O); 1689(C=O ring); 1619(C=N) and 1603(C=C).	1.0(t, 3H, CH_3CH_2); 2.1(s, 2H, -$COCH_2$-); 3.0(s, 1H, pyrimidine H-5); 3.4(q, 2H, CH_3CH_2-); 5.2(s, br., 3H, three NH) and 7.1–8.2(m, 5H, ArH's).
18c	3340, 3310, 3226; 3189 (NH_2 and NH); 3078 (arom- atic CH); 2977(sat., CH); 1690(C=O ring); 1612 (C=N) and 1600(C=C).	2.0(s, 2H, -$COCH_2$-); 3.2(s, 1H, pyrimidine H-5); 4.9(s, br., 3H, three NH); 6.0(s, br., 2H, NH_2) and 7.0–8.1(m, 5H, ArH's).
19	3222, 3189 (NH); 3082 (aromatic CH); 2979(sat., CH); 1695(C=O); 1610 (C=N) and 1601(C=C).	2.1(s, 2H, -$COCH_2$-); 3.2(s, 1H, pyrimidine H-5); 5.8(s, br., 2H, two NH) and 6.9–7.8(m, 5H, ArH's).
21a	3197 (NH); 3077(aromatic CH); 1688(C=O); 1617 (C=N) and 1600(C=C).	2.1(s, 2H, -$COCH_2$-); 3.2(s, 1H, pyrimidine H-5); 6.0(s, br., 2H, two NH) and 6.9–7.8(m, 5H, ArH's).
21b	3188(NH); 2975(sat., CH); 3079(aromatic CH); 1690(C=O); 1615 (C=N) and 1604(C=C).	1.1(s, 3H, CH_3); 2.9(s, 1H, pyrimidine H-5) and 7.0–8.2(m, 6H, NH and ArH's).
22a	3182(NH); 3077(aromatic CH); 1692(C=O); 1617 (C=N) and 1601(C=C).	3.1(s, 1H, pyrimidine H-5); 4.2(s, 2H, -$COCH_2$-); 5.3(s, br., 1H, NH) and 7.0–8.1(m, 10H, ArH's).
22b	3190(NH); 3069(aromatic CH); 2978(sat., CH); 1690 (C=O); 1615 (C=N) and 1600 (C=C).	1.0(s, 3H, CH_3); 3.2(s, 1H, pyrimidine H-5); 4.4(s, 2H, -$COCH_2$-); 5.5(s, br., 1H, NH) and 6.9–7.8(m, 5H, ArH's).
25	3379, 3282, 3190(NH_2 NH) ; 3075(aromatic CH); 1689 (C=O); 1617 (C=N) and 1600 (C=C).	2.8(s, 1H, pyrimidine H-5); 3.4(s, 1H, pyrazole H-4); 4.8(s, br., 2H, two NH); 5.6(s, br., 2H, NH_2) and 7.0–7.9(m, 5H, ArH's).
27a	3212, 3182(NH) ; 3070(aromatic CH); 1693 (C=O); 1612 (C=N) and 1600(C=C).	3.1(s, 1H, pyrimidine H-5); 4.9(s, br., 1H, pyrimidine NH); 5.4(s, 1H, -CH=N-); 6.9–8.1(m, 10H, ArH's) and 9.8(s, br., 1H, NH, -NH-N=).
27b	3219, 3180(NH); 3079(aromatic CH); 1692 (C=O); 1616 (C=N) and 1600(C=C).	3.0(s, 1H, pyrimidine H-5); 5.1(s, br., 1H, pyrimidine NH); 5.6(s, 1H, -CH=N-); 7.0–7.9(m, 9H, ArH's) and 9.9(s, br., 1H, NH, -NH-N=).
27c	3223, 3193(NH); 3082(aromatic CH); 1689 (C=O); 1615 (C=N) and 1602(C=C).	3.1(s, 1H, pyrimidine H-5); 4.8(s, br., 1H, pyrimidine NH); 5.5(s, 1H, -CH=N-); 6.5–7.7(m, 8H, furyl and ArH's) and 10.1(s, br., 1H, NH, -NH-N=).
30a	3223, 3187(NH); 3079(aromatic CH); 1695 (C=O); 1613 (C=N) and 1602(C=C).	3.0(s, 1H, pyrimidine H-5); 5.6(s, br., 2H, two NH) and 6.9–7.8(m, 5H, ArH's).
30b	3217, 3195(NH); 3082(aromatic CH); 1689 (C=O); 1615(C=N) and 1603(C=C).	3.2(s, 1H, pyrimidine H-5) and 6.9–8.1(m, 7H, two NH and ArH's).

ponding 2-(3',5'-dimethyl-1'-pyrazolyl)-6-phenyl-pyrimidine-4-one (**15**) *via* the non-isolable intermediate **14**. The reaction is most probably proceeded through dehydration in two successive steps. By considering the data of IR, ^1H NMR and elemental analyses, structure **15** was confirmed. Moreover, its mass spectrum gave *m/z*= 266, corresponding to the molecular weight of a molecular formula $C_{15}H_{14}N_4O$ of the assigned structure (*cf.* Chart 2).

Compound **5** reacted with chloroacetone (**10a**), α-chloroacetylacetone (**10b**) and ethyl α-chloroacetoacetate (**10c**) to afford compounds **16a-c**, respectively, *via* dehydrochlorination. Compounds **16a-c** were cyclized in ethanolic sodium ethoxide to afford the corresponding pyrimido[2,1-c]-1,2,4-triazines **17a-c**, respectively. Structures **16a-c** and **17a-c** were established based on IR, ^1H NMR and elemental analyses (*cf.* Tables I and II). Moreover, the mass spectra of **16a-c** gave *m/z*=258, 300 and

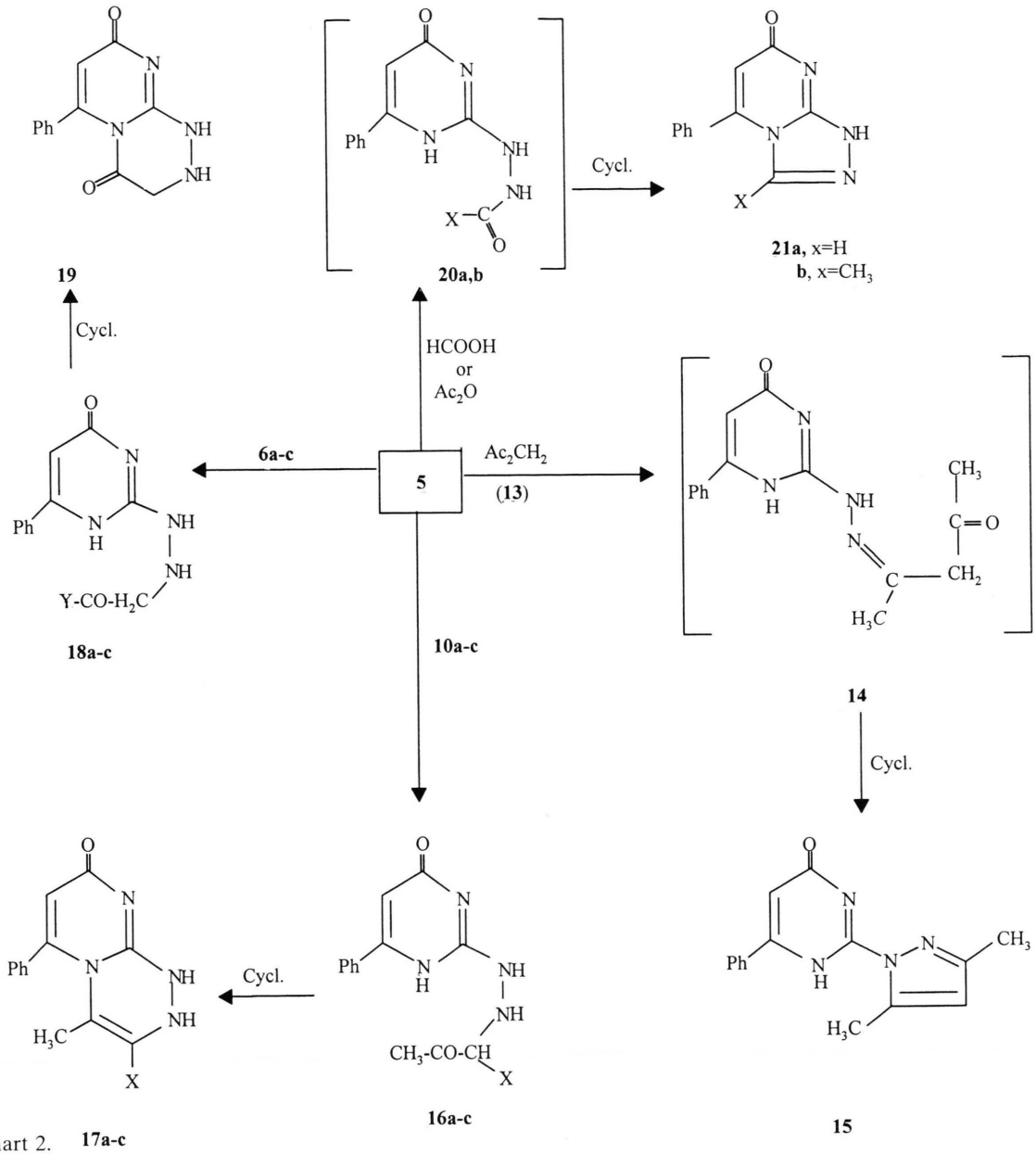

Chart 2.

330, corresponding to the molecular weights of the molecular formulas $C_{13}H_{14}N_4O_2$, $C_{15}H_{16}N_4O_3$ and $C_{16}H_{18}N_4O_4$ of the assigned structures (*cf.* Chart 2). The mass spectra of the cyclization products **17a-c** gave *m/z*=240, 282 and 312, respectively, corresponding to the molecular weights of the molecular formulas $C_{13}H_{12}N_4O$, $C_{15}H_{14}N_4O_2$ and $C_{16}H_{16}N_4O_3$ of the assigned structures (*cf.* Chart 2). The peaks at *m/z*=240, 282 and 312, of the **17a-c** confirmed that the cyclization of **16a-c** proceeded through dehydration in each case.

Similarly, compound **5** reacted with chloroacetic acid (**6a**), ethyl chloroacetate (**6b**) and chloroacetamide (**6c**) to afford compounds **18a-c** via dehydrochlorination. Compounds **18a-c** cyclized in ethanolic hydrochloric acid to afford one and the

same product **19**. Depending on the data given from IR, ^{1}H NMR and elemental analyses (Tables I and II), compound **19** could be formulated as 4-phenylpyrimido[2,1-c]-1,2,4-triazine. The mass spectra of **18a-c** gave *m/z*=260, 288 and 259, corresponding to the molecular weights of the molecular formulas $C_{12}H_{12}N_4O_3$, $C_{14}H_{16}N_4O_3$ and $C_{12}H_{13}N_5O_2$ of the assigned structures (*cf.* Chart 2). However, the mass spectrum of **19** gave *m/z*= 242, corresponding to the molecular weight of a molecular formula $C_{12}H_{10}N_4O_2$ of the assigned structure (*cf.* Chart 2). The appearance of a peak at *m/z*=242 for compound **19** confirmed that cyclization of **18a-c** proceeded via elimination of water, ethanol and ammonia in a respective manner.

Furthermore, compound **5** reacted with, both, formic acid and acetic anhydride under the same experimental conditions to afford directly the corresponding triazolo[4,3-a]pyrimidines **21a,b**, respectively. It is important to report here that all trials to isolate the intermediates **20a,b** failed under a variety of conditions. Structures **21a,b** were

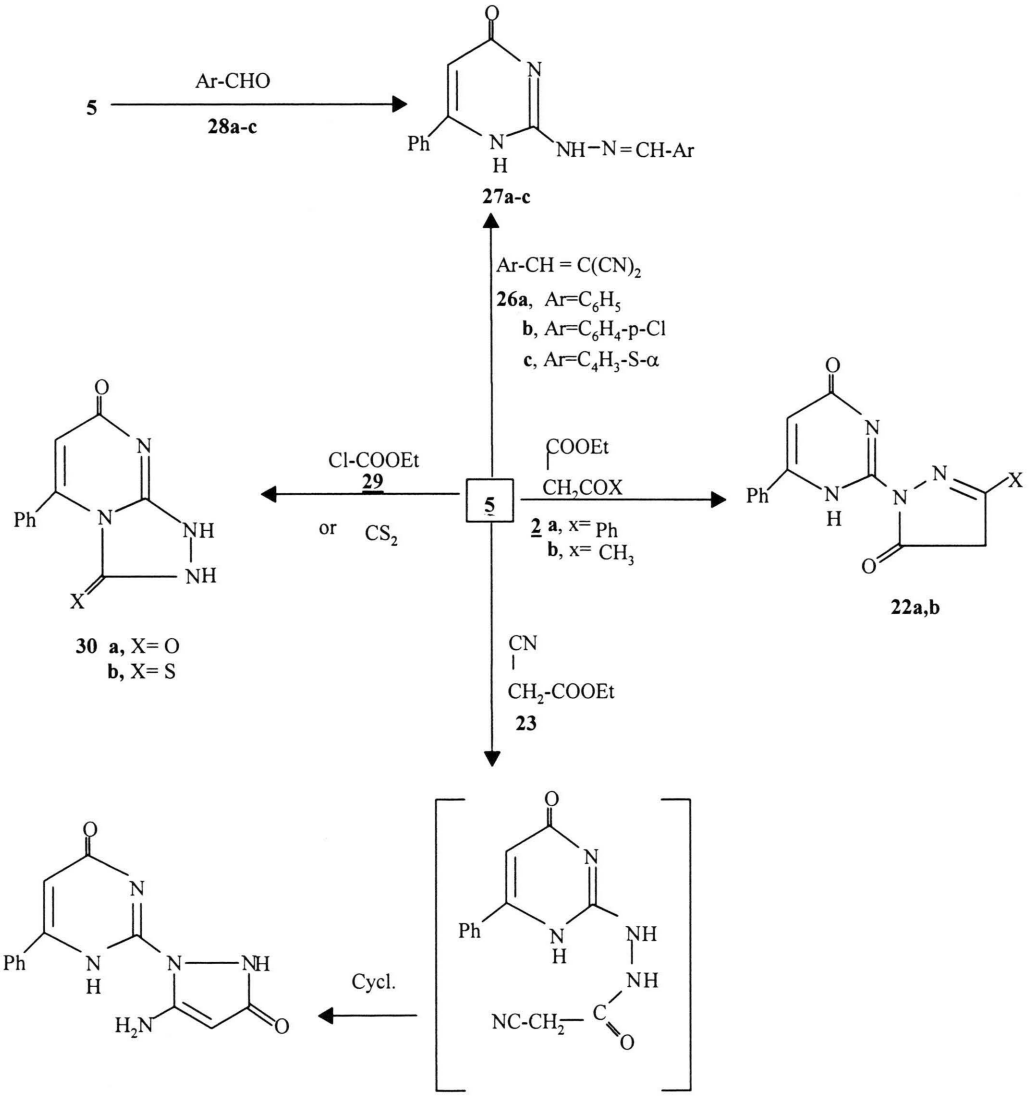

Chart 3.

established, based on IR, ^{1}H NMR and elemental analyses (Tables I and II).

The synthon **5** reacted with ethyl benzoylacetate (**2a**) and ethyl acetoacetate (**2b**) in ethanolic sodium ethoxide to afford directly the corresponding 2-(1'-pyrazolyl)pyrimidine-4-one derivatives **22a,b**, respectively. Structure **22a,b** was confirmed, based on IR, ^{1}H NMR and elemental analyses (*cf.* Tables I and II). Moreover, their mass spectra gave *m/z*=330 and 268, representing the molecular weights of the molecular formulas $C_{19}H_{14}N_4O_2$ and $C_{14}H_{12}N_4O_2$ of the assigned structures (*cf.* Chart 3).

Furthermore, compound **5** reacted with ethyl cyanoacetate (**23**) under the same experimental conditions to afford the corresponded 6-phenyl-2-(5'-amino-1'-pyrazol-3'-one)pyrimidine-4-one **25** *via* the non-isolable open chain compound **24**. The structure **25** was established based on the data given from IR, ^{1}H NMR and elemental analyses (*cf.* Tables I and II). Moreover, its mass spectrum gave the same *m/z*=269 which corresponded to a molecular weight of a molecular formula $C_{13}H_{11}N_5O_2$ for **25** (*cf.* Chart 3). It is remarkable to report here that the IR spectrum of **25** has no bands of a CN group, while the newly born NH_2 group was detected (*cf.* Table II).

Work was extended to shed more light on the chemical reactivity of **5**. Thus, it has been found that compound **5** reacted with the cinnamonitriles **26a-c** to give the corresponding hydrazones **27a-c**, which were most probably formed *via* an arylidene group exchange reaction. The formation of hydrazones **27a-c** was confirmed by their preparation *via* another route. Thus, compound **5** reacted with the appropriate aromatic aldehydes **28a-c** in ethanol containing the catalytic amount of triethylamine to afford the same previously obtained products **27a-c** respectively. The structures of **27a-c**, obtained from the two routes were confirmed based on IR, ^{1}H NMR and elemental analyses (*cf.* Tables I and II).

Work was also directed to synthesize the biologically active triazolo[4,3-a]pyrimidine derivatives **30a,b** through the reaction of **5** with ethyl chloroformate (**29**) and carbon disulfide. Thus, compound **5** reacted with **29** in ethanolic sodium ethoxide while with carbon disulfide in pyridine the corresponded triazolopyrimidines **30a,b** were obtained. The structures **30a,b** were confirmed, based on IR, ^{1}H NMR and elemental analyses (*cf.* Tables I and II). Moreover, their mass spectra gave *m/z*=228 and 244, corresponding to the molecular weights of the molecular formulas $C_{11}H_8N_4O_2$ and $C_{11}H_8N_4SO$ of the assigned structures (*cf.* Chart 3).

Biological Activity

Using the disc-diffusion technique [10], some of the newly synthesized heterocyclic derivatives were tested *in vitro* against some Gram-positive, Gram-negative bacteria, yeast and filamentous fungi. The results obtained, indicated that some compounds (**9**, **12b**, **30b** and **22a,b**) were active towards Gram-positive, some are active towards Gram-negative bacteria (**15** and **30b**), while others (**8** and **11**) are active towards both. On the other hand, compounds **12b** and **16b** were active toward yeast, and compounds **5** and **15** showed antifungal activity (*cf.* Table III).

Experimental

All melting points are uncorrected. The IR spectra in KBr discs were recorded on Perkin-Elmer FT-IR type 4 and Pye Unicam SP-1100 spectrophotometers. The ^{1}H NMR spectra were recorded on Varian EM 390–90 MHz, Varian Gemini, 200 and Brucker WP-80 spectrometers using $CDCl_3$, DMSO-d_6 and $(CD_3)_2CO$ as solvents and TMS as an internal standard. Chemical shifts are expressed as δ ppm units. Mass spectra were recorded on Hewlett-Packard GC-MS type 2988 series A using the DIP technique at 70 eV. Microanalyses were performed at the Microanalytical Center of Cairo University, using a Perkin-Elmer 2400 CHN Elemental Analyzer.

Synthesis of **4, 7a-d, 11a-c, 16a-c** *and* **18a-c**: *General procedure:*

A solution of **3** and/or **5** (0.01 mole) and each of ethyl iodide, **6a-c** and **10a-c** in ethanolic sodium ethoxide (prepared by dissolving 0.01 atom of sodium metal in 50 ml of ethanol) was heated under reflux for 5–7 h (TLC). The reaction mixture was then cooled and poured onto ice-cold water. The solid products obtained after acidification with hydrochloric acid were filtered off, washed with water, then crystallized from ethanol, to afford **4**, **7a-d**, **11a-c**, **16a-c** and **18a-c**, respectively (*cf.* Tables I and II).

Table III. The antimicrobial activity of the tested new compounds.

Comp.	Gram + ve bacteria			Gram −ve bacteria	Yeast	Filament. fungi	
	Staph. A.	Bacil. S.	Microco. L.	Esch. coli.	Such. cerv.	Asp. fum.	Asp. terr.
4	++	−	+	−	+	−	−
5	+	+	++	−	+	++	++
7c	++	−	−	+	−	−	−
7d	+	−	+	−	−	−	−
8	+	++	+	++	−	−	+
9	++	++	+	++	−	+	−
11b	+	−	+	−	−	+	−
12b	++	++	+	−	++	−	−
15	++	−	+	+++	+	++	++
16a	+	−	+	+	−	−	−
16b	+	−	+	−	++	+	−
17a	+	+	+	−	−	−	−
17b	+	−	−	−	−	−	−
19	+	−	++	+	−	−	+
21b	+	++	−	+	−	+	−
22a	++	+++	++	++	−	+	+
22b	++	++	+++	++	−	+	+
30a	+	+	+	++	−	−	+
30b	++	++	++	+++	−	+	++

The minimal inhibitory concentration (MIC) has been used as a parameter to express the antimicrobial activity of each compound as shown:

Activity		MIC
Highly active	= +++	10–30 μg / ml
Moderately active	= ++	35–50 μg / ml
Slightly active	= +	55–75 μg / ml
Inactive	= −	> 75 μg / ml

Synthesis of **8, 9, 12a-c, 17a-c** *and* **19***:*
General procedure:

A solution of **7a-c, 7d, 11a-c, 16a-c** and **18a-c** in ethanol (50 ml) and hydrochloric acid (3 ml) was heated under reflux for 5 h. The reaction mixture was cooled and then poured onto ice-cold water. The separated products was then washed with water and crystallized from ethanol to yield **8**, **9**, **12a-c**, **17a-c** and **19** (*cf.* Tables I and II).

Synthesis of **5***:*

A mixture of **3** or **4** (0.01 mole) was heated under reflux with excess of hydrazine hydrate (≅15 ml) until the odor of H_2S or CH_3SH ceased. The solid product obtained after pouring onto ice-cold water were filtered off and crystallized from ethanol to give **5** in each case (*cf.* Tables I and II).

Synthesis of **21a,b***:*

A mixture of **5** (0.01 mole) and each of formic acid and acetic anhydride (35 ml of each) was heated under reflux for 10 h. The solid products obtained after pouring onto ice-cold water were filtered off, washed with water and crystallized from the proper solvent to afford **21a,b** respectively (*cf.* Tables I and II).

Synthesis of **15** *and* **22b***:*

A mixture of **5** (0.01 mole) and acetyl acetone (**13**) and ethyl acetoacetate (**2b**) was heated, each in a mixture of ethanol: acetic acid, 1:3, under reflux for 5 h. The solid products obtained after cooling and pouring onto ice-cold water were filtered off, washed with water and crystallized from the proper solvent to give **15** and **22b** respectively (*cf.* Tables I and II).

Synthesis of **30a***:*

A mixture of **5** (0.01 mole) and ethyl chloroformate (**29**), 0.01 mole, in absolute ethanol (50 ml), containing a catalytic amount of triethylamine (0.5 ml), was heated under reflux for 5 h. The solid product obtained after cooling and acidification

with acetic acid was filtered off and crystallized from ethanol to afford **30a** (*cf.* Tables I and II).

Synthesis of **30b**:

A mixture of **5** (0.01 mole) and carbon disulfide in pyridine was heated under reflux for 5 h. The reaction mixture was then cooled and acidified with hydrochloric acid. Solid product obtained was filtered off, washed with water and crystallized from ethanol to afford **30b** (*cf.* Tables I and II).

Synthesis of **27a-c, 22a** *and* **25**:
General procedure:

A mixture of **5** (0.01 mole) and **26a-c, 2a** and **23** each (0.01 mole of each) in glacial acetic acid (50 ml) was heated under reflux for 5 h. The solid products obtained after cooling were filtered off, washed with water and crystallized from the proper solvent to afford **27a-c**, **22a** and **25** respectively (*cf.* Tables I and II).

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