Hikmat N. Al-Jallo (1) and Muhamad A. Muniem

Department of Chemistry, Atomic Energy Commission, NRI, Tuwaitha, Baghdad, Iraq

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Ethyl phenylpropiolate reacted with 2-aminobenzothiazoles, benzimidazoles, thiazoline and thiazole to give the corresponding fused 2-oxopyrimidines. 2-Mercaptobenzimidazole reacted with ethyl phenylpropiolate to give 4-phenyl-2*H*-1-thiapyrimido[1,2-*a*]benzimidazol-2-one in very good yield. The thiones, methylthio iodides and the hydrobromides of some of the products were prepared. Analysis of the nmr spectra of the benzothiazole and benzimidazole products and their 3-deuterio analogs showed that the proton at position 6 is shielded and absorbs together with the proton at position 3 near δ 6.0 ppm. The nmr and ir spectral data of all the products are tabulated and discussed.

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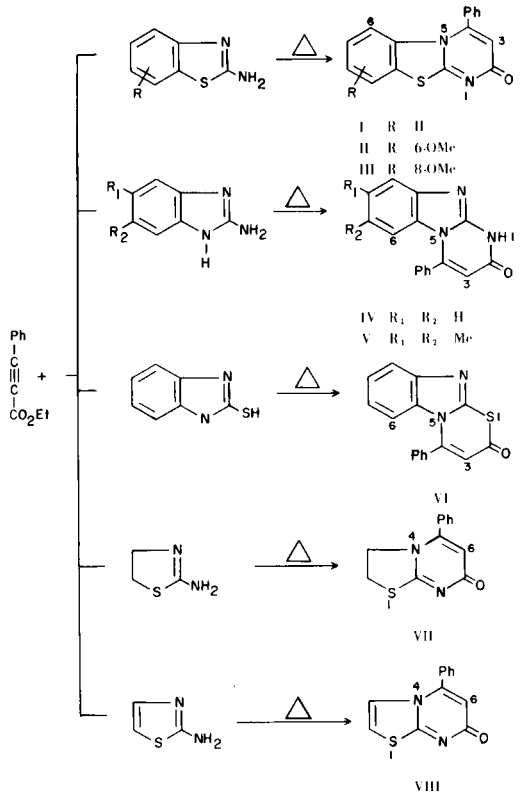
A number of synthetic methods have been reported for the preparation of condensed pyrimidine compounds (2) due to their biological importance (3). Basically these methods involve the condensation of 2-aminoheterocycles with certain carbonyl derivatives. Among these, 2-aminothiazole reacted with acetoacetic and β-aminocrotonic esters (4), or ethoxymethylenemalonate (5) to give the appropriate 5*H*-pyrimido[2,1-*b*]thiazol-5-ones instead of the 7-oxo derivatives which were incorrectly assigned previously (6). Similarly, a number of 4*H*-pyrimido[2,1-*b*]benzothiazol-4-ones were prepared from 2-aminobenzothiazoles and β-aminocrotonic ester (4), alkoxymethylenemalonate (7) or ethyl acetoacetate (8,9). On the other hand, only limited information is available on the synthesis of the 2-oxo derivatives. Few examples of the latter compounds have been reported, and the products have been obtained in variable yields from the reaction of 2-aminoheterocycles with acetylenic acid or its ethyl ester (9). Moreover, while 2-aminobenzimidazole reacted with α,β-unsaturated carboxylic acid chloride or esters to give pyrimido[1,2-*a*]-benzimidazol-2(1*H*)ones, ethoxymethylenematonate or β-ketocarboxylic acid derivatives gave the corresponding 4-oxo derivatives (10).

Recently, we have prepared a number of 2*H*-pyrido-[1,2-*a*]pyrimidin-2-ones by heating 2-aminopyridines with ethyl phenylpropiolate at appropriate temperatures (11). In this work, we report the condensation of ethyl phenylpropiolate with a number of 2-aminobenzothiazoles, benzimidazoles, thiazoline and thiazole. Moreover, the condensation of 2-mercapto and 2-hydroxybenzimidazole with the acetylenic ester were attempted (Scheme I).

We have found that when 2-aminobenzothiazole, and its 4- and 6-methoxy substituted analogs were heated with ethyl phenylpropiolate, the corresponding 2*H*-pyrimido-[2,1-*b*]benzothiazol-2-ones (I-III) were obtained in good yields (Table I). The possibility for the formation of the 4-oxo derivatives was excluded on the basis of nmr spectra, as the latter compounds are characterized by the absorption of a deshielded proton near δ 9 ppm. This proton was assigned to be the proton at position 6, and the deshielding was attributed to the anistropy of the

Scheme I



Scheme II

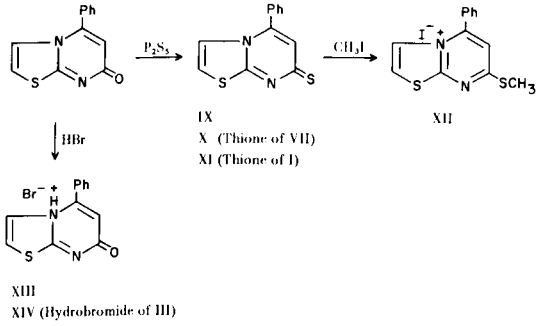


Table I

Fused Pyrimidine Compounds

Compound Number	Reaction Temperature (Time, hours)	Yield %	M.p. °C Solvent of Recrystallization	Formula		Analysis % C	H	N
I (a)	120-130 (0.5)	44.0	239-240 (c)	$C_{16}H_{10}N_2OS$	Calcd.	69.06	3.60	10.07
					Found	69.27	3.52	9.94
II	150-160 (0.5)	64.0	236-237 (c)	$C_{17}H_{12}N_2O_2S$	Calcd.	66.23	3.90	9.09
					Found	66.24	3.94	8.92
III	150-160	84	255-256 (c)	$C_{17}H_{12}N_2O_2S$	Calcd.	66.23	3.90	9.09
					Found	65.90	3.97	9.00
IV	180-200 (11) (g)	71.4	>350 (f)	$C_{15}H_{11}N_3O$	Calcd.	73.36	4.21	16.04
					Found	73.79	4.44	15.94
V	180-200 (12) (g)	86.4	>350 (f)	$C_{17}H_{15}N_3O$	Calcd.	74.74	5.19	14.53
					Found	74.93	5.36	14.33
VI	180-200 (11) (g)	86.5	225-227 (d)	$C_{15}H_{10}N_2OS$	Calcd.	69.06	3.60	10.07
					Found	69.25	3.80	9.91
VII (b)	110-120 (0.5)	89.0	243-244 (c)	$C_{12}H_{10}N_2OS$	Calcd.	62.61	4.35	12.17
					Found	62.95	4.44	12.52
VIII	100-120 (0.5)	47.0	252-253 (c)	$C_{12}H_8N_2OS$	Calcd.	63.16	3.51	12.28
					Found	62.95	3.71	12.22
IX		81.2	250-252 (d)	$C_{12}H_8N_2S_2$	Calcd.	59.02	3.28	11.48
					Found	59.17	3.38	11.56
X		71.4	264-266 (d)	$C_{12}H_{10}N_2S_2$	Calcd.	58.50	4.06	11.37
					Found	58.66	4.19	11.35
XI		94	343-344 (d)	$C_{16}H_{10}N_2S_2$	Calcd.	65.31	3.40	9.52
					Found	65.47	3.56	9.69
XII		50	256-258 (d)	$C_{13}H_{11}IN_2S_2$	Calcd.	40.42	2.85	7.26
					Found	40.68	3.05	7.08
XIII		64.1	305-308 (e)	$C_{12}H_9BrN_2OS$	Calcd.	46.75	2.68	9.06
					Found	46.40	3.10	8.87
XIV		70.0	315-317 (e)	$C_{16}H_{11}BrN_2OS$	Calcd.	52.44	3.34	7.18
					Found	52.21	3.77	6.78

(a) Lit. (9), m.p. 237-238°, 25% yield. (b) Lit. (9), m.p. 191-194°, 3% yield. (c) Recrystallized from benzene. (d) Recrystallized from acetone. (e) Recrystallized from ethanol. (f) Recrystallized from butanol. (g) In ethanol.

carbonyl group (7). The nmr spectra of the compounds obtained from benzothiazoles (I-III) and benzimidazoles (IV and V) showed that there are two protons in the region between δ 6.0-6.7 ppm (Table II). One of these protons, which absorbed as a sharp singlet, is attributed to the proton at position 3 and the other is due to one of the aromatic protons. The assignment of the proton at position 3 was based on comparing the spectra with a corresponding one for the 3-deuterio compounds which were prepared for this purpose. On the other hand, the assignment of the other proton was based on a comparison of the spectra of different substituted compounds. The nmr spectra of the 6-methoxy compound (II) showed only singlet absorption due to the proton at position 3, which disappeared in the spectrum of the 3-deuterio compound. This indicated that the proton which absorbed in the same region as the proton at position 3, was in fact the one at position 6. Further evidences were obtained from the nmr spectrum of the 8-methoxy compound (III) which showed singlet absorption at δ 6.2 ppm due to the proton at position 3, and doublet absorption at δ 6.02 ppm due to the proton at position 6 (Table II). It was noticed that the presence of the methoxy group at position 6 resulted in a deshielding of the proton at position 3 (Table II). Moreover, in the ir spectra, the carbonyl stretching frequency is shifted to higher and lower values in the 6-methoxy and 8-methoxy derivatives as compared with compound I (Table III).

The shielding effect observed in the proton at position 6 in the above compounds (I-III) is most likely due to the ring current of the phenyl group at position 4. Constructing Courtauld atomic models for these molecules

Table II

Nmr Spectral Data δ (ppm) of Fused Pyrimidines

Compounds Number	H_2	H_3	H_6	H_7	H_8	H_9	C_6H_5
I (c)		6.26 (s)	6.1 (s)	← 6.8 — 7.8 (m, 8H) →			
II (c)		6.72 (s)	4.0 (s) (CH_3)	← 7.0 — 8.2 (m, 8H) →			
III (c)		6.2 (s)	6.02 (d) J = 9 Hz	6.55 (dd) J = 9, 3 Hz	3.76 (s) (CH_3)	7.12 (d) J = 3 Hz	7.3-7.7 (m, 5H)
IV (d)		5.92 (s)	6.02 (d) J = 8 Hz	← 6.7 — 7.6 (m, 3H) — 7.68 (s) →			
(b)		6.84 (s)	6.41 (d) J = 8 Hz	← 6.6 — 8.0 (m, 8H) →			
V (d)		5.86 (s)	5.76 (s)	1.98 (s) (CH_3)	2.3 (s) (CH_3)	7.28 (s)	7.68 (s)
(b)		6.88 (s)	6.08 (s)	2.1 (s)	2.34 (s)	7.56 (s)	7.76 (s)
VI (d)		6.57 (s)	6.78 (d)	← 6.8 — 7.8 (m, 8H) →			
(c)		6.4 (s)	6.8 (d)	← 6.9 — 8.0 (m, 8H) →			
VII (c)	3.38 (t) J = 6 Hz	4.2 (t) J = 6 Hz	5.95 (s) (a)				7.5 (s)
VIII (c)	6.83 (dd) J = 8, 4 Hz	7.18 (dd) J = 18, 4 Hz	6.3 (s) (a)				7.52 (s)
(d)	7.2 (d)	7.36 (d)	6.14 (s)				7.65 (s)
IX (d)	overlapped with C_6H_5		7.0 (s) (a)				7.4-7.8 (m, 7H)
X (c)	3.48 (t)	4.28 (t)	6.7 (s) (a)				7.55 (s)
XI (d)		7.2 (s)	6.3 (d) J = 8 Hz	← 6.8 — 7.8 (m, 8H) →			
XII (d)	← 8.2 (q, 2H) →		8.05 (s) (a)	2.8 (s) (SCH_3)			7.7 (s)
XIII (d)	← 8.4 (s, 2H) →		6.8 (s)				7.68 (s)
XIV (d)			8.3 (s)	overlapped with C_6H_5	3.7 (s) (CH_3)	7.0	8.5 (m, 7H)

(a) Due to the different numbering system of these compounds, this proton corresponds to H_3 in compounds I-VI. (b) After addition of deuterium chloride to the nmr samples of the compounds. (c) In deuteriochloroform. (d) In deuteriodimethyl sulfoxide.

showed clearly that the proton at position 6 is in fact projected above the plane of the phenyl group at position 4. The above shielding effect is to a certain extent similar to that observed for the central methylene groups of [1.8]paracyclophane (12). Further evidence for this argument is obtained from the fact that no such shielding effect was noticed in the same compounds when the phenyl group was replaced by hydrogen (9).

The reaction of 2-aminobenzimidazole and its 5,6-dimethyl derivatives with ethyl phenylpropiolate was carried out and the resulting pyrimido[1,2-*a*]benzimidazol-2(1*H*)-ones (IV and V) were obtained in good yields (Table I). The exclusion of the 4-oxo derivative, the assignment of the proton at position 3, and the shielding of the proton at position 6 could be explained as mentioned above for compounds I-III. While the proton at position 6 showed doublet absorption at δ 6.02 ppm in compound IV, it adsorbed as a singlet at δ 5.76 ppm in the 7,8-dimethyl compound (V) (Table II). Addition of deuterium chloride to the nmr samples of compounds IV and V resulted in an appreciable deshielding of most of the protons, especially the one at position 3. The ir spectra of these compounds (IV and V) showed a strong carbonyl stretching absorption at 1680 cm^{-1} beside other absorption bands listed in Table III.

Heating of 2-mercaptobenzimidazole and ethyl phenylpropiolate afforded 4-phenyl-2*H*-1-thiapyrimido[1,2-*a*]-benzimidazol-2-one (VI) in very good yield (Table I). As mentioned above, the proton at position 6 of compound VI is also shielded and absorbed in the same region as the proton at position 3. Generally, most of the nmr protons of VI are deshielded in comparison with the parent

Table III

Ir Spectral Data of Fused Pyrimidines

Compound Number	ν max/cm^{-1} (a)								
I	1650 (vs),	1660 (sh),	1580 (m),	1520 (s),	1450 (s),	1260 (m)			
II	1690 (vs),	1650 (sh),	1570 (m),	1530 (s),	1490 (s),	1380 (s),	1290 (s)	1040 (s)	
III	1650 (sh),	1638 (vs),	1580 (m),	1510 (s),	1490 (vs),	1290 (s),	1270 (s),	1030 (s)	
IV	3430 (br),	2700 (br),	1680 (vs),	1665 (sh),	1460 (s),	1418 (s),	1280 (m),	1260 (m)	
V	3430 (br),	2700 (br),	1680 (vs),	1465 (s),	1418 (s)				
VI	1679 (vs),	1650 (sh),	1470 (s),	1440 (s),	1358 (s),	1304 (s)			
VII	1630 (s),	1610 (sh),	1570 (m),	1508 (s),	1445 (m),	1415 (s),	1190 (m),	1055 (m)	
VIII	1635 (vs),	1608 (s),	1570 (s),	1510 (s),	1480 (vs),	1450 (s),	1415 (s),	1220 (m)	
IX	1610 (s),	1590 (s),	1556 (m),	1460 (s),	1390 (m),	1330 (m),	1235 (m),	1140 (s)	
X	1595 (sh),	1580 (m),	1560 (s),	1494 (m),	1465 (vs),	1255 (m),	1170 (m),	1120 (s)	
XI	1610 (s),	1590 (s),	1570 (m),	1490 (vs),	1480 (vs),	1320 (m),	1270 (m),	1135 (s)	
XII	1602 (vs),	1545 (m),	1490 (m),	1470 (vs),	1345 (s)	1315 (m),	1250 (m),	1130 (vs)	
XIII	2500 (br),	1726 (vs),	1570 (m),	1470 (m),	1418 (vs),	1325 (vs),	1325 (s),	1300 (s),	1250 (m)
XIV	2450 (br),	1720 (sh),	1700 (sh),	1680 (vs),	1625 (m),	1370 (s)			

(a) Potassium bromide disc spectra.

pyrimidone compound (IV) (Table II). This effect could be explained on the assumption that introduction of a sulfur atom usually enhances the ring current, probably due to d-orbital conjugation (13). Several attempts to condense 2-hydroxybenzimidazole with ethyl phenylpropiolate under different experimental conditions failed, and in all cases unreacted hydroxylimidazole was isolated.

Furthermore, 2-aminothiazoline and 2-aminothiazole reacted with ethyl phenylpropiolate to give 5-phenyl-7*H*-pyrimido[2,1-*b*]thiazolin-7-one (VII, 89%) and 5-phenyl-7*H*-pyrimido[2,1-*b*]thiazol-7-one (VIII), respectively (Table I). Although the ir and nmr spectra (Tables II and III) of compound VIII are similar to those reported before, our compound melted at 252-253° and was obtained in 47% yield as compared with 191-194° (3%) (9). In the nmr spectra of compounds VII and VIII, the assignment of the proton at position 6 (which corresponds to the proton at position 3 in compounds I-V) was similar to the procedure already described. It was noticed that in deuteriodimethylsulfoxide, the protons of compounds VIII were deshielded compared with those in deuteriochloroform. Moreover, the deshielding value of the proton at position 2 is as twice of the value at position 3. When compounds VIII, VII and I were heated in pyridine with phosphorus pentasulfide, the corresponding thiones (IX-XI) were obtained (Table I, Scheme II). The ir spectra of these thiones showed strong absorption bands between 1120 and 1140 cm^{-1} due to the C=S stretching vibrations (14). In comparing the nmr spectra of IX-XI with the parent carbonyl compounds, appreciable deshielding of most of the protons was observed, especially for the proton at position 3 in compound XI and at position 6 for compounds IX and X. Further deshielding of the protons was noticed in the spectra of the methylthio iodide compound (XII) and the hydrobromides of compounds IV and VIII (Table II). The ir spectra of these hydrobromides (XIII and XIV) showed relatively higher carbonyl stretching frequencies as compared with the parent compounds VIII and III, respectively (Table III). Such a frequency increase confirmed that protonation had in fact occured at the *N*-atom rather than the *O*-atom, which resulted in an increase of the double bond character of the carbonyl group (15).

EXPERIMENTAL

Ir spectra were measured with an IR 10 instrument and H-nmr spectra were determined with a Varian T-60A instrument (tetramethylsilane as the internal standard). Microanalytical samples were analysed using 185B HP CHN analyser. Melting points were determined on a Köfler block and are uncorrected. The purity of the reaction products were checked by tlc.

Condensation of Ethyl Phenylpropiolate and 2-Aminoheterocycles. General Procedure.

Ethyl phenylpropiolate (0.05 mole) and 2-aminoheterocycles (0.05 mole) were heated for a specified time and temperature indicated in Table I. The products obtained were recrystallized to give 4-phenyl-2*H*-pyrimido[2,1-*b*]benzothiazol-2-ones (I-III) and [1,2-*a*]benzimidazol-2(1*H*)ones (IV and V) from 2-aminobenzthiazole and benzimidazole, respectively. Moreover, 5-phenyl-7*H*-pyrimido[2,1-*b*]thiazolin-7-one (VII) and thiazol-7-one (VIII) were obtained from 2-aminothiazoline and 2-aminothiazole, respectively (Table I). The condensation of 2-mercaptobenzimidazole with ethyl phenylpropiolate was similarly carried out to give 4-phenyl-2*H*-1-thiapyrimido[1,2-*a*]benzimidazol-2-one (VI) in very good yield (Table I). On the other hand, several attempts to condense 2-hydroxybenzimidazole with ethyl phenylpropiolate failed, and in all cases the starting 2-hydroxybenzimidazole was recovered. These attempts included heating the reactants in the absence or presence of different solvents. The temperature was raised up to 200° for different time intervals up to 50 hours.

Furthermore, sodium ethoxide was used as a catalyst and the mixture was refluxed in ethanol or benzene for variable time intervals, and still no reaction occured.

Preparation of 3-Deuterio-4-phenylpyrimido[1,2-*a*]benzimidazol-2(1*H*)ones and [2,1-*b*]benzothiazol-2-ones.

The above procedure and conditions (Table I) used for the preparation of compounds I-V were used except that 2 ml. of deuterium oxide (99.95% D) was added to the reactants. Distillation of the water *in vacuo* followed by recrystallization of the residue from the appropriate solvents afforded the 3-deuterio derivatives of the above compounds. Similarly, the 6-deuterio derivatives of compounds VII and VIII were prepared.

Preparation of the Thiones of Compounds I, VII and VIII.

Fused pyrimidines (I, VII or VIII; 1 g.) in pyridine (50 ml.) and phosphorus pentasulfide (1 g.) were heated for a half an hour at 150° and then cooled. The reaction mixture was cooled and poured onto ice water and extracted with chloroform. The chloroform layer was dried over magnesium sulfate and evaporated to dryness to give an orange-yellow solid. Recrystallization from acetone afforded pure samples of the thiones (XI-IX).

Preparation of the Methylthio Iodide of VIII.

To compound VIII (0.2 g.) dissolved in benzene (250 ml.), methyl iodide (5 ml.) was added and the mixture was left at room temperature overnight. The product was filtered and recrystallized from acetone to give a pure sample of compound XII (Table I).

Preparation of the Hydorbromides of III and VIII.

Dry hydrogen bromide was passed through a chloroform solution of compound III or VIII until no further white solid products were formed. Recrystallization of the products from ethanol afforded pure samples of the hydrobromides XIV and XIII (Table I).

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