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REACTIONS WITH ∝ -THIOCARBAMOYLCINNAMONITRILES: SYNTHESIS OF PYRAZOLO [1,5-a] PYRIMIDINES.

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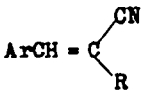
Abstract- Whereas each of ∝ -thiocarbamoyl- and ∝ -cyanomalononitrile derivatives 1a and 1d reacted with benzamidine (2) hydrochloride to give only 4-amino-6-(4-chlorophenyl)-2-phenyl-5-pyrimidine-carbonitrile (5a), they react with 5-amino-3-phenylpyrazole (6) to yield the two differently substituted pyrazolo[1,5-a]pyrimidines 7 and 8, respectively. Compounds 1a,c reacted also with ∝ -haloketones to produce the substituted thiazoles 10. The structures of the newly synthesized compounds were proved by spectral studies and chemical routes.

Our previous studies were concerned with the synthesis of some pyrimidine derivatives by reactions of ∝ -substituted cinnamonitriles with S-methylisothiourea and desulphurisation of the reaction products with hidrazine followed by cyclisation with bifunctional reagents[1,2]. In view of the continued interest in the uses of ∝ -substituted cinnamonitriles in the synthesis of heterocycles[3-5] and because of the considerable biological and medicinal activities of pyrimidine[6,7], azolopyrimidine[8,9] and thiazole[10,11] derivatives, we report here the simple syntheses of polysubstituted pyrimidine and some pyrazolo [1,5-a] pyrimidine derivatives. In addition we described the synthesis of polysubstituted thiazoles. Thus, the ∝ -thiocarbamoylcinnamonitriles (1a,b) reacted with benzamidine (2) hydrochloride, in pyridine in the presence of anydrous sodium acetate, to give products for which structures 3, 4 and 5 seem possible, but structure 5 was preferred based on spectral data and the synthesis of 5a by an alternative route via the reaction of 1d with 2 .



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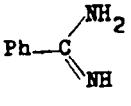
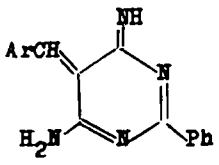


2

1	Ar	R
a	C_6H_4Cl-p	$CSNH_2$
b	$C_6H_4N(CH_3)_2$-p	$CSNH_2$
c	$C_6H_4OCH_3$-p	$CSNH_2$
d	C_6H_4Cl-p	CN
e	$C_6H_4OCH_3$-p	CN



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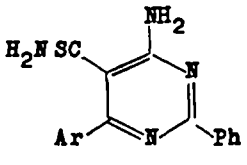

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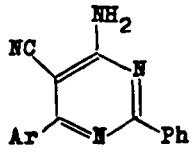


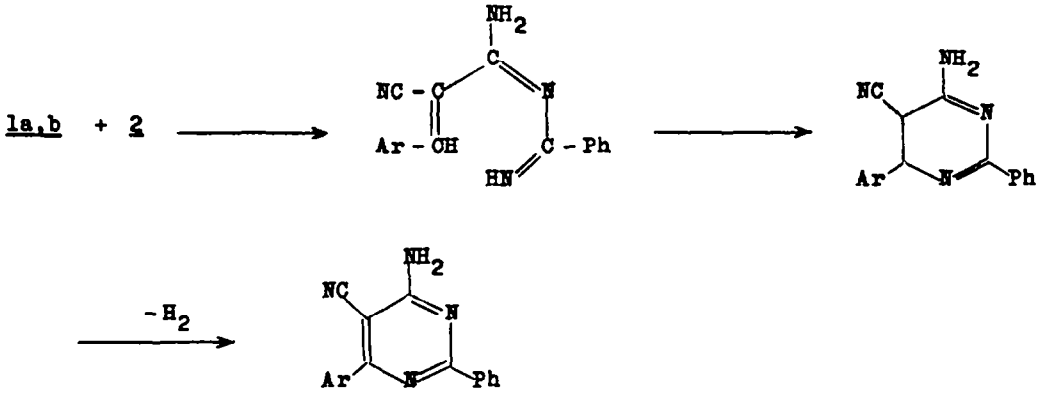
5

5	Ar
a	C_6H_4Cl-p
b	$C_6H_4N(CH_3)_2$-p

1d + 2 ⟶ 5a

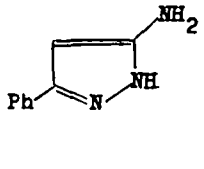
The formation of 5 from 1a,b and 2 is assumed to proceed via an initial elimination of H_2S followed by cycloaddition and dehydrogenation as shown in Scheme 1.

Scheme 1



5

Similar to the behaviour of 1a,b with 2, compounds 1a,c reacted with 5-amino-3-phenylpyrazole (6) to yield the 7-amino-5-aryl-2-phenylpyrazolo [1,5-a] pyrimidine-6-carbonitriles (7a,b) rather than the isomeric structure 8.



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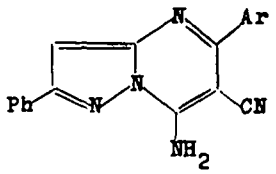

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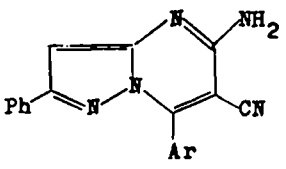


8

7,8	Ar
a	C_6H_4Cl-p
b	$C_6H_4OCH_3$-p

Structure 7 was inferred from the facts that :- (a) Characteristic data in the IR and ^{1}H-NMR spectra (Experimental). (b) It was reported by El-Nagdi et al[12] that the reaction of 6 with benzalmalononitrile is accomplished by addition of the ring nitrogen atom in 6 to the activated double bond in the nitrile compound to yield the 7-phenyl derivative of 8. (c) Compounds 8 were synthesized by an alternative route and found to be different from 7 (See below). (d) The ^{1}H-NMR spectra of 7a,b displayed broad singlet at about δ 3.5 ppm (NH_2), while chemical shifts of the amino groups in 8a,b appeared at about 8.9 ppm (See below).

The formation of 7 in the above reaction is assumed to proceed in a similar manner like that in Scheme 1, via an initial elimination of H_2S from the proton of the ring nitrogen atom in 6 and the mercapto group in 1a,c , followed by cyclisation and dehydrogenation.

Compound 6 reacted with 1d,e, in pyridine in the presence of anhydrous sodium acetate to give the pyrazolo[1,5-a]pyrimidine derivatives (8a,b), which were found to be different from the isomeric compounds 7a,b.

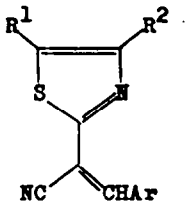
The IR spectra of 8 showed an absorption band at about 2220 (CN), while the ^{1}H-NMR spectra of 8a,b gave characteristic data.

When compounds 1a,c were treated with the α-haloketones 9a-c, in ethanol in the presence of catalytic amounts of piperidine, the thiazole derivatives 10a-e were obtained in good yield. The IR spectra of 10a-e displayed an absorption band at about 2220 (CN).

$R^1CHX\,CO\,R^2$

9

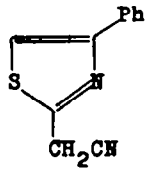
9	R^1	R^2	X
a	hH	C_6H_5	Br
b	H	$CH_2CONHPh$	Br
c	CONHPh	CH_3	Cl



10

10a

NH_2-NHR



11

10	R^1	R^2	Ar
a	H	C_6H_5	$C_6H_4OCH_3$-p
b	H	$CH_2CONHPh$	C_6H_4Cl-p
c	H	$CH_2CONHPh$	$C_6H_4OCH_3$-p
d	CONHPh	CH_3	C_6H_4Cl-p
e	CONHPh	CH_3	$C_6H_4OCH_3$-p

In support of structure 10 for the reaction products, compound 10a, as a typical α-,β-unsaturated nitrile, underwent fission at the exocyclic ethylenic double bond on heating with hydrazine or phenylhydrazine, in absolute ethanol, to give 2-cyanomethyl-4-phenylthiozole (11) together with the dianisalhydrazine or anisaldehyde - phenylhydrazone. Compound 11 is identical to an authentic sample prepared by Schafer's method[13].

EXPERIMENTAL

All melting points are uncorrected.- IR spectra were recorded (KBr) on a Pye Unicam SP-1000 spectrophotometer.- ^{1}H-NMR spectra were obtained in $(CD_3)_2SO$ with a Varian EM-390 spectrometer with $SiMe_4$ as internal standard, and chemical shifts are expressed as δ values. Microanalytical data were performed by the Microanalytical Center at Cairo University.

Reactions of 1a,b with 2 Hydrochloride.- General procedure: A mixture of 2 hydrochloride (1.57g, 0.01 mol), an equimolecular amount of each of 1a,b (0.01 mol), anhydrous fused sodium acetate (1.64 g, 0.02 mol) and pyridine (25 ml) was heated under reflux for 5 h and left at room temperature for 3 h. The solution was poured into water; the solid product was collected by filtration and crystal-ised from the proper solvent to give 5a,b.

4-Amino-6-(4-chlorophenyl)-2-phenyl-5-pyrimidine carbonitrile (5a): Yellow crystals from dioxane; yield 2.32 g (76%); m.p. 225°C.- IR (KBr): 3400, 3350 (NH), 2220 (CN), 1650 (NH_2).- ^{1}H-NMR: δ = 7.4-7.7 (m, 5H, aromatic H), 7.85-8.3 (m, 4H, aromatic H), 8.55 (broad s, 2 H, disappears after deuterium oxide exchange, NH_2). Found: C 66.5; H 3.5; Cl 11.7; N 18.1. Calc.for $C_{17}H_{11}ClN_4$ C 66.56; H 3.62; Cl 11.70; N 18.10%.

4-Amino-6-[4-(dimethylamino)phenyl]-2-phenyl-5-pyrimidinecarbonitrile (5b):Greenish yellow crystals from dilute dioxane; yield 1.92 g (61%); m.p. 220°C.- IR (KBr):3300, 3200 (NH), 2215 (CN), 1640 (NH_2). Found: C 72.3; H 5.3; N 22.2. Calc. for $C_{19}H_{17}N_5$:C 72.36; H 5.43; N 22.20%.

Reaction of 1d with 2 .- 1.62 g (0.01 mol) of 1d were mixed with 1.57 g (0.01 mol) of 2, 1.64 g (0.02 mol) of anhydrous sodium acetate and 20 ml of pyridine . The reaction mixture was heated under reflux for 7 h and then proceeded as mentioned above in the General procedure to give 2.46 g (80%) of 5a, m.p. 225°C, not depressed when mixed with that obtained by the above procedure.

Reactions of 1a,c-e with 6.- General procedure: A solution of 1.59 g (0.01 mol) of 6 and an equimolecular amount of each of 1a,c-e (0.01 mol) in 25 ml of pyridine was refluxed for 10 h. The reaction mixture was left to cool and poured into cold water. The upper layer was decanted and the residue was triturated with dilute hydrochloric acid. The solid that separated was filtered off, washed thoroughly with water and crystallised from the proper solvent to give 7a,b and 8a,b.

7-Amino-5-(4-chlorophenyl)-2-phenylpyrazolo[1,5-a]pyrimidine-6-carbonitrile (7a): Yellow crystals from acetic acid- yield 2.1 g (60%); m.p. > 300°C.- IR (KBr): 3300, 3200 (NH), 3020 (CH), 2220 (CN), 1650 (NH_2).- ^{1}H-NMR: δ = 3.5 (s, 2H, disappears after deuterium oxide exchange, NH_2), 6.95 (s, 1H, CH), 7.05-7.25 (m, 5H, aromatic H), 7.3-7.78 (m, 4H, aromatic H). Found: C 65.9; H 3.6; Cl 10.3; N 20.2. Calc. for $C_{19}H_{12}ClN_5$: C 65.99; H 3.50; Cl 10.26; N 20.25%.

7-Amino-5-(4-methoxyphenyl)-2-phenylpyrazolo[1,5-a]pyrimidine-6-carbonitrile (7b): Yellow crystals from dioxane; yield 2.1 g (63%); m.p. 278°C.- IR (KBr): 3350, 3320 (NH), 3000 (CH), 2220 (CN), 1650 (NH_2).- ^{1}H-NMR: δ = 3.52 (s, 2H, disappears after deuterium oxide exchange, NH_2), 4.1 (s, 3H, OCH_3), 7.1 (s, 1H, CH), 7.2-7.35 (m, 5H, aromatic H), 7.4-7.8 (m, 4H, aromatic H). Found: C 70.6; H 4.3; N 20.5. Calc. for $C_{20}H_{15}N_5O$: C 70.37; H 4.43; N 20.52%.

5-Amino-7-(4-chlorophenyl)-2-phenylpyrazolo[1,5-a]pyrimidine-6-carbonitrile (8a): Yellow crystals from dimethylformamide; 2.4 g (70%); m.p. > 300°C.- IR (KBr):3450, 3300 (NH). 2950 (CH), 2220 (CN), 1650 (NH_2).- ^{1}H-NMR: 7.21 (s, 1H, CH), 7.5-7.9(m, 5H, aromatic H), 7.95-8.45 (m, 4H, aromatic H), 8.9 (s, 2H, disappears after deuterium oxide exchange, NH_2). Found: C 66.2; H 3.6; Cl 10.5; N 20.2; Calc. for $C_{19}H_{12}ClN_5$: C 65.99; H 3.50; Cl 10.26; N 20.25%.

5-Amino-7-(4-methoxyphenyl)-2-phenylpyrazolo[1,5-a]pyrimidine-6-carbonitrile (8b): Yellow crystals from dilute dimethylformamide; yield 2.6 g (75%); m.p. 244°C.- IR (KBr): 3430, 3320 (NH), 2960 (CH), 2220 (CN), 1660 (NH_2).- ^{1}H-NMR: δ = 3.92 (s,3H, OCH_3), 7.1 (s, 1H, CH), 7.15-7.3 (m, 3H, aromatic H), 7.4-7.8 (m, 2H, aromatic H), 7.9-8.35 (m, 4H, aromatic H), 8.85 (s, 2H, disappears after deuterium oxide exchange, NH_2). Found: C 70.5; H 4.5; N 20.3. Calc. for $C_{20}H_{15}N_5O$: C 70.37; H 4.43; N 20.52%.

Reactions of 1a,c with 9a-c.- General procedure: To a solution of 1a,c (0.01 mol) in absolute ethanol (50 ml) was added an equimolecular amount of each of 9a-d (0.01 mol) and a catalytic amount of piperidine (0.5 ml). The reaction mixture was refluxed for 2 h and the precipitate separated, on hot or after cooling, was collected and crystallised from the proper solvent.

α-(4-Phenyl-2-thiazolyl)-p-methoxycinnamonitrile (10a): Orange crystals from ethanol; yield 3.02 g (95%); m.p. 127°C.- IR (KBr): 3040 (CH), 2218 (CN),-^{1}H-NMR: δ = 3.85 (s, 3, OCH_3), 7.05 (s, 1, CH), 7.2 (s, 1, CH), 7.3-7.65 (m, 4, aromatic H , 7.95-8.38 (m, 5, aromatic H). Found: C 71.9; H 4.4; N 8.7; S 10.0. Calc. for $C_{19}H_{14}N_2OS$: C 71.68, H 4.43, N 8.80; S 10.06% .

α-(4-Phenylcarbamoylmethyl-2-thiazolyl)-p-chlorocinnamonitrile (10b): Yellow crystals from dioxane; yield 3.3 g (87%) m.p. 192°C.- IR (KBr): 3240 (NH), 3040 (CH), 2218 (CN), 1670 (CO). ^{1}H-NMR:δ = 3.95 (s, 2, CH_2), 7.2 (s, 1, CH), 7.5-8.0 (m, 4, aromatic H), 8.1-8.35 (m, 5, aromatic H), 10.4 (s, 1, NH). Found: C 63.3; H 3.8; Cl 9.2; N 11.0; S 8.4. Calc. for $C_{20}H_{14}ClN_3OS$:C 63.23; H 3.71; Cl 9.34; N 11.07; S 8.43%.

α-(4-Phenylcarbamoylmethyl-2-thiazolyl)p-methoxycinnamonitrile (10c): Yellow crystals from dilute dimethylformamide; yield 3.18 g (85%); m.p. 180°C.- IR (KBr): 3320 (NH), 3090 (CH), 2222 (CN), 1660 (CO).- ^{1}H-NMR:δ = 4.0 (s, 2, CH_2), 4.1 (s, 3, OCH_3), 7.2 (s, 1, CH), 7.5 (s, 1, CH), 7.65-7.95 (m, 4, aromatic H), 8.07-8.29 (m, 5, aromatic H), 10.3 (s, 1, NH), Found: C 67.3; H 4.5; N 11.0; S 8.5; Calc. for $C_{21}H_{17}N_3O_2S$: C 67.18; H 4.56; N 11.20; S 8.53%.

α-(4-Methyl-5-phenylcarbamoyl-2-thiazolyl)-p-chlorocinnamonitrile (10d): Greenish yellow crystals from dioxane; yield 3.04 g (80%); m.p. 198°C. IR (KBr): 3350(NH), 3020 (CH), 2220 (CN), 1660 (CO). ^{1}H-NMR:δ = 2.75 (s, 3, CH_3), 7.15 (s, 1, CH), 7.2-7.6 (m, 4, aromatic H), 8.0-8.4 (m, 5, aromatic H), 10.3 (s, 1 NH). Found: C 63.1; H 3.7; Cl 9.1; N 11.1; S 8.6. Calc. for $C_{20}H_{14}ClN_3OS$: C 63.23 ; H 3.71; Cl 9.34; N 11.07%.

α-(4-Methyl-5-phenylcarbamoyl-2-thiazolyl)-p-methoxycinnamonitrile (10e): Yellow crystals from dilute dioxane; yield 3.38 g (90%); m.p. 186°C.- IR (KBr): 3340(NH), 3000 (CH), 2220 (CN), 1670 (CO).- ^{1}H-NMR:δ = 2.75 (s, 3, CH_3), 3.9 (s, 3, OCH_3), 7.2 (s, 1, CH), 7.3-7.6 (m, 4, aromatic H), 8.0-8.4 (m, 5, aromatic H), 10.3 (s, 1, NH). Found: C 67.2; H 4.5; N 11.1; S 8.5; Calc. for $C_{21}H_{17}N_3O_2S$: C 67.18, H 4.56; N 11.20; S 8.53%.

Reaction of 10a with hydrazine and phenylhydrazine.- General procedure: A solution of 1.59 g (0.005 mol) of 10a in ethanol (30 ml) was treated with an equimolecular amount (0.005 mol) of each of hydrazine hydrate or phenylhydrazine. The reaction mixture was heated under reflux for 5 h, left to cool and then poured

into water. Few drops of hydrochloric acid were added whereupon precipitation occured. The solid that separated was filtered off, crystallised from ethanol and found to be dianisalhydrazine, m.p. 168°C or anisaldehyde - phenylhydrazone, m.p. 120°C, respectively. The filtrate was extracted with ether and the ethereal layer was washed with water, dried with anhydrous sodium sulphate and evaporated. The residual was triturated with petroleum ether (40-60°) and crystallised from ethanol to give 11a, m.p. 62°C, not depressed when mixed with an authentic sample[13].

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