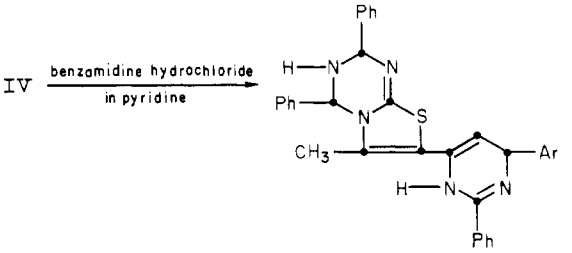
Table IV. 7-(4-Aryl-2-phenylpyrimidinyl)thiazolo-*s*-triazines (VII)

compd	mp, °C	solvent[a]	yield, %
VIIa	232	A	73
b	219	N	65
c	224	A	68
d	237	D	61
e	213	E	77

[a] A = acetic acid; N = nitrobenzene; D = dioxane; E = ethanol.

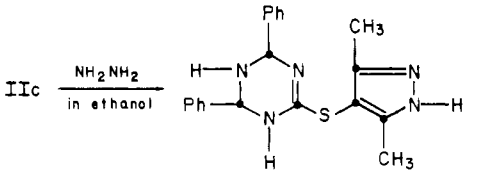
in the δ 7.5–8.25 region (15 H).

7-(4-Aryl-4,5-dihydro-2-phenylpyrimidin-6-yl)-6-methyl-2,4-diphenyl-2,3,4-trihydrothiazolo[3,2-a]-1,3,5-triazines (VII). A solution of IV (0.01 mol) and benzamidine hydrochloride (0.01 mol) in pyridine (20 mL) was heated under reflux for 6 h and left overnight. The separated substances were filtered and crystallized (see Table IV). The IR spectrum of VII shows an absorption band at 3200 cm^{-1} (NH).



VIIa, Ar = C_6H_5
b, Ar = $C_6H_4OCH_3$-*p*
c, Ar = C_6H_4Cl-*p*
d, Ar = $C_6H_4NO_2$-*m*
e, Ar = $C_6H_4N(CH_3)_2$-*p*

2-(3,5-Dimethylpyrazol-4-ylthio)-4,6-diphenyl-3,4,5,6-tetrahydro-1,3,5-triazine (VIII). To a solution of IIc (0.005 mol) in ethanol (20 mL), hydrazine hydrate (98%, 0.5 mL) was added and the reaction mixture was refluxed for 3 h and left to cool; compound VIII was separated, filtered off, and crystallized from acetic acid: mp 206 °C; yield 65%. The IR spectrum of VIII shows a broad band at 3200 cm^{-1} (3 NH). The ^1H NMR of compound VIII showed the methyl groups as two singlets at δ 2.35 (3 H) and δ 2.85 (3 H), the =CH proton at δ 6.15 (1 H), the two CH protons as a singlet at δ 4.2 (2 H), the three NH protons at δ 9.5 (3 H), and the aromatic protons as a multiplet in the δ 7.45–8.15 region (10 H).



VIII

Registry No. Ia, 61582-10-3; Ib, 61582-11-4; Ic, 87102-21-4; II'a, 87102-22-5; II'b, 87102-23-6; II'c, 87102-24-7; II'd, 87102-25-8; II'e, 87102-26-9; II'f, 87102-27-0; II'g, 87102-28-1; II'h, 87102-29-2; II'i, 87102-30-5; IIIa, 87102-31-6; IIIb, 87102-32-7; IIIc, 87102-33-8; IIId, 87102-34-9; IIIe, 87102-35-0; IIIf, 87102-36-1; IIIg, 87114-29-2; IIIh, 87102-37-2; IIIi, 87102-38-3; IVa, 87102-39-4; IVb, 87102-40-7; IVc, 87102-41-8; IVd, 87102-42-9; IVe, 87102-43-0; IVf, 87102-44-1; V, 87102-45-2; VIa, 87102-46-3; VIb, 87102-47-4; VIc, 87102-48-5; VIIa, 87114-30-5; VIIb, 87114-31-6; VIIc, 87135-99-7; VIId, 87114-32-7; VIIe, 87114-33-8; VIII, 87102-49-6; C_6H_5CHO, 100-52-7; *p*-$CH_3OC_6H_4CHO$, 123-11-5; *p*-ClC_6H_4CHO, 104-88-1; *m*-$NO_2C_6H_4CHO$, 99-61-6; *p*-$NO_2C_6H_4CHO$, 555-16-8; *p*-$(CH_3)_2NC_6H_4CHO$, 100-10-7; H_2NNH_2, 302-01-2; phenacyl bromide, 70-11-1; *p*-methylphenacyl bromide, 619-41-0; α-chloroacetylacetone, 1694-29-7; phenylhydrazine, 100-63-0; hydroxylamine hydrochloride, 5470-11-1; benzamidine hydrochloride, 1670-14-0.

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Activated Nitriles in Heterocyclic Synthesis. Synthesis of Several New Pyrimidine and Pyridazine Derivatives

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Several new pyrimidine, pyridazine, and pyridine derivatives were obtained from 2-(ethoxycarbonyl)-3-aminopentenedinitrile (I) as starting component.

Malononitrile, ethyl cyanoacetate, and their derivatives are among the most commonly utilized intermediates in heterocyclic synthesis (*1*, *2*). Recently, Junek et al., (*3*) have reported the formation of 2-(ethoxycarbonyl)-3-aminopentenedinitrile (I) via simple addition of ethyl cyanoacetate to malononitrile. This product seemed to be an excellent candidate for utility in heterocyclic synthesis. In conjunction with our interest in the utility of activated nitriles in heterocyclic synthesis (*4*, *5*) we report here the utility of I for preparation of a variety of polyfunctionally substituted heterocyclic derivatives of potential synthetic and biological importance. Thus, it has been found that I coupled with benzenediazonium chloride to yield the hydrazone II. Compound II, cyclized into the diacetyl derivative III on refluxing with acetic anhydride. Compound IV was obtained on refluxing II in acetic acid.

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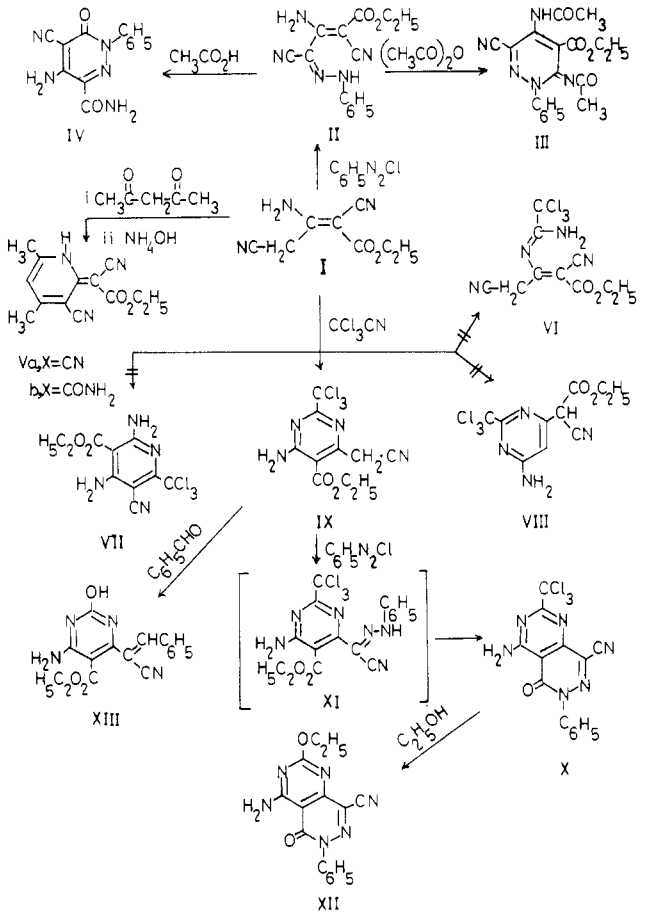
Table I. List of the Newly Synthesized Compounds

compd (color)[a]	mp, °C	yield, %	crys solv	IR, cm^{-1}	^1H NMR, ppm
II (yellow)	130	80	*b*	3450 (NH_2), 2990 (CH_3), 2200 (CN), 1660 (ester CO)	1.33 (t, 3 H, CH_3), 4.3 (q, 2 H, CH_2), 7.1-7.6 (m, 5 H, C_6H_5), 7.85-8.15 (3 H, NH_2 and NH, br)
III (red)	200	78	*c*	3420-3200 (NH_2, br), 2220 (CN), 1660-1630 (CO bands)	1.33 (t, 3 H, CH_3), 2.5 and 2.7 (two singlets, $2COCH_3$), 4.2 (q, 2 H, CH_2), 7.2-7.9 (m, 5 H, C_6H_5), 8.8 (s, 1 H, NH)
IV (orange)	300	65	*c*	3400-3250 (NH_2 and amide NH_2), 2220 (CN), 1680-1610 (CO, amide CO, and C=N, br)	
Va (orange)	205	85	*d*	3100 (NH), 2990 and 2810 (CH_3 bands), 2220 and 2210 (CN bands), 1660 (ester CO)	1.3 (t, 3 H, CH_3), 2.45 and 2.55 (two singlets, $2CH_3$), 4.3 (q, 2 H, CH_2), 6.9 (s, 1 H, pyridine H-3), 14.6 (s, 1 H, NH)
Vb (red)	252	70	*e*	3280 and 3225 (amide NH_2 and NH), 2220 (CN), 1680-1620 (CO and C=C, br)	
IX (brown)	180	60	*b*	3350 and 3250 (NH_2), 2220 (CN), 1630 (ester CO)	1.16 (t, 3 H, CH_3), 3.0 (m, 6 H, $2CH_2$ and NH_2)
X (red-brown)	123	70	*b*	3440 and 3360 (NH_2), 2220 (CN), 1660 (CO)	3.35 (s, 2 H, NH_2), 7.3-7.9 (m, 5 H, C_6H_5)
XII (red-brown)	95	67	*b*	3440 and 3360 (NH_2), 2220 (CN), 1665 (CO)	
XIII (red)	145	72	*b*	3540-3020 (OH and NH_2, br), 2220 (CN), 1670-1520 (ester CO, C=N, C=C)	

[a] Satisfactory elemental analyses were submitted. [b] Ethanol. [c] Dioxane. [d] Dioxane-ethanol. [e] DMF.



Similar to the reported ready condensation of 2-amino-1,1,3-tricyanopropene with acetylacetone (*6*), compound I condensed with the same reagent to yield the pyridine derivative Va. The latter converted into Vb on treatment with ammonium hydroxide.

Compound I also reacted with trichloroacetonitrile in ethanolic triethylamine to yield a 1:1 adduct. Four theoretically possible isomeric structures were considered (cf. Structures VI–IX). The acyclic structure VI could be readily eliminated on the basis of the stability of the reaction product on boiling in acetic acid (*7*). The pyrimidine structure IX could be readily established on the basis of the ^1H NMR spectra which revealed an active methylene group at δ 3.0 and on the basis of the ready condensation of the reaction product with benzaldehyde and benzenediazonium chloride. Thus, compound IX coupled with benzenediazonium chloride to yield the pyridazino[4,5-*d*]pyrimidine derivative X via intermediacy of the hydrazone XI. The trichloromethyl molety in IX was readily attacked by nucleophilic reagents. Thus, compound IX, on refluxing in ethanol, afforded the ethoxy derivative XII. A similar observation has been recently reported (*8*). Compound IX also condensed with benzaldehyde to yield the benzylidene derivative XIII.

Experimental Section

All melting points are uncorrected. IR spectra were recorded (KBr) with a Pye-Unicam SP 1100 spectrophotometer. ^1H NMR spectra were obtained on an EM-390 90-MHz spectrophotometer using Me_4Si as internal indicator and chemical shifts are expressed in ppm. Analytical data were obtained from the analytical data unit at Cairo University.

3-Amino-2-(ethoxycarbonyl)-4-(phenylhydrazono)pentenedinitrile (II). A solution of 0.01 mol of benzenediazonium chloride was added to a stirred solution of I (0.01 mol) in ethanol containing 5 g of sodium acetate. The reaction mixture was left at room temperature for 15 min and the resulting solid product was collected by filtration and crystallized from the proper solvent (cf. Table I).

Reaction of II with Acetic Anhydride. A solution of II (2 g) in acetic anhydride (40 mL) was heated under reflux for 10 h. The solvent was then evaporated in vacuo and the remaining material was poured into water. The solid product, so formed, was collected by filtration and crystallized from the proper solvent (cf. Table I).

Reaction of II with Acetic Acid. A suspension of II (2.0 g) in acetic acid (30 mL) was refluxed for 3 h and then evaporated in vacuo. The remaining product was collected by filtration and crystallized from the proper solvent (cf. Table I).

3-Cyano-4,6-dimethyl-1,2-dihydro-2-(disubstituted methylene)pyridine (Va,b). A solution of I (0.01 mol) in

ethanol (30 mL) was treated with acetylacetone (0.01) and piperidine (1 mL). The reaction mixture was heated under reflux for 2 h. The solid, formed while the solution was still boiling, was filtered off and crystallized from the proper solvent (cf. Table I).

Compound Vb was obtained by heating a mixture of Va (1.0 g) and ammonium hydroxide (5 mL; 20–21%) on a water bath for 30 min and washing the solid product, formed after cooling, with hydrochloric acid and water.

4-Amino-6-(cyanomethyl)-5-(ethoxycarbonyl)-2-(trichloromethyl)pyrimidine (IX). To a suspension of I (0.01 mol) in toluene (50 mL) and dry ether (100 mL) was added 0.01 mol of sodium metal. The reaction mixture was left overnight at room temperature. To this suspension was added 0.01 mol of trichloroacetonitrile and the reaction mixture was heated under reflux for 4 h. The solvent was then evaporated under vacuum and the remaining solid product was collected by filtration and crystallized from the proper solvent (cf. Table I).

Condensation of IX with Benzenediazonium Chloride. A slution of 0.01 mol of benzenediazonium chloride was added to a solution of IX (0.01 mol) in DMF (50 mL). The reaction mixture was heated for 5 min and then left to cool. The solid product, so formed, was collected by filtration and crystallized from the proper solvent (cf. Table I).

Condensation of IX with Benzaldehyde. A solution of IX (0.01 mol) in ethanol (50 mL) was treated with benzaldehyde (0.01 mol) and piperidine (1 mL). The reaction mixture was refluxed for 5 h and then evaporated in vacuo. The remaining solid product was collected by filtration and crystallized from the proper solvent (cf. Table I).

7-Amino-3-cyano-1,8-dihydro-5-ethoxy-8-oxo-1-phenylpyridazino[4,5-d]pyrimidine (XII). A solution of IX (2.0 g) in ethanol (50 mL) was heated under reflux for 2 h and then left to cool. The solid product, so formed, was collected by filtration and crystallized from the proper solvent (cf. Table I).

Registry No. I, 64544-92-9; II, 87831-18-3; III, 87831-19-4; IV, 87831-20-7; Va, 87831-21-8; Vb, 87831-22-9; IX, 87831-23-0; X, 87831-24-1; XII, 87831-25-2; XIII, 87831-26-3; benzenediazonium chloride, 100-34-5; acetic anhydride, 108-24-7; acetic acid, 64-19-7; acetylacetone, 123-54-6; benzaldehyde, 100-52-7.

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